

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208216Orig1s000**

**LABELING**

## HIGHLIGHTS OF PRESCRIBING INFORMATION

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

**AZACITIDINE for injection, for subcutaneous or intravenous use**  
**Initial U.S. Approval: 2004**

### INDICATIONS AND USAGE

Azacitidine for Injection 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 (CMML) (1).

### DOSAGE AND ADMINISTRATION

- The recommended starting dose for the first treatment cycle, for all patients regardless of baseline hematology values, is Azacitidine for Injection 75 mg/m<sup>2</sup> daily for 7 days to be administered by subcutaneous injection or intravenous 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<sup>2</sup> 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).
- Monitor patients for hematologic response and for renal toxicity; delay or reduce dosage as appropriate (2.3, 2.4, 2.5).

### DOSAGE FORMS AND STRENGTHS

- For Injection; 100 mg, lyophilized powder in single-dose vial for reconstitution (3).

### CONTRAINDICATIONS

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

### WARNINGS AND PRECAUTIONS

- Anemia, neutropenia and thrombocytopenia: Monitor complete blood counts frequently (CBC) (5.1).
- Hepatic toxicity: Patients with severe preexisting hepatic impairment are at higher risk for toxicity (5.2).
- Renal impairment: Monitor patients with renal impairment for toxicity since azacitidine and its metabolites are primarily excreted by the kidneys (5.3).
- Embryo-Fetal toxicity: Can cause fetal harm when administered to a pregnant woman. Advise females and males of reproductive potential of the potential risk to a fetus and to avoid pregnancy (5.4, 8.1, 8.3).

### ADVERSE REACTIONS

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

To report SUSPECTED ADVERSE REACTIONS, contact Actavis at 1-800-432-8534 or FDA at 1-800-FDA-1088 or [www.fda.gov/medwatch](http://www.fda.gov/medwatch).

### USE IN SPECIFIC POPULATIONS

Lactation: Advise not to breastfeed (8.2).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 04/2016

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## FULL PRESCRIBING INFORMATION

### 1 INDICATIONS AND USAGE

#### 1.1 Myelodysplastic Syndromes (MDS)

Azacitidine for Injection 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 (CMML).

### 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<sup>2</sup> subcutaneously or intravenously, daily for 7 days. Patients should be premedicated for nausea and vomiting.

Complete blood counts, liver chemistries and serum creatinine should be obtained prior to first dose.

#### 2.2 Subsequent Treatment Cycles

Cycles should be repeated every 4 weeks. The dose may be increased to 100 mg/m<sup>2</sup> if no beneficial effect is seen after 2 treatment cycles and if no toxicity other than nausea and vomiting has occurred. Treat patients 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 greater than or equal to 3 x10<sup>9</sup>/L, ANC greater than or equal to 1.5 x10<sup>9</sup>/L, and platelets greater than or equal to 75 x10<sup>9</sup>/L, adjust the dose as follows, based on nadir counts for any given cycle:

| Nadir Counts                   |                                      | % Dose in the Next Course |
|--------------------------------|--------------------------------------|---------------------------|
| <u>ANC (x10<sup>9</sup>/L)</u> | <u>Platelets (x10<sup>9</sup>/L)</u> |                           |
| <0.5                           | <25                                  | 50%                       |
| 0.5 to 1.5                     | 25 to 50                             | 67%                       |
| >1.5                           | >50                                  | 100%                      |

- For patients whose baseline counts are WBC less than 3 x10<sup>9</sup>/L, ANC less than 1.5 x10<sup>9</sup>/L, or platelets less than 75 x10<sup>9</sup>/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<br>% decrease in counts from baseline | Bone Marrow Biopsy Cellularity at Time of Nadir (%) |          |     |
|---|---|----------|-----|
|   | 30 to 60  | 15 to 30 | <15 |
| 50 to 75<br>>75   | % Dose in the Next Course                           |          |     |
|   | 100   | 50       | 33  |
|   | 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 greater than 25% above the nadir and rising. If a greater than 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 Serum Electrolytes and Renal Toxicity

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 *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 Azacitidine for Injection

Azacitidine for Injection is a cytotoxic drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing Azacitidine for Injection suspensions [see *How Supplied/Storage and Handling (16)*].

If reconstituted Azacitidine for Injection 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 Azacitidine for Injection vial is single-dose 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

Azacitidine for Injection 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. Do not filter the suspension after reconstitution. Doing so could remove the active substance.

**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. When Azacitidine for Injection is reconstituted using water for injection that has not been refrigerated, the reconstituted product may be held under refrigerated conditions (2°C to 8°C, 36°F to 46°F) for up to 12 hours. When Azacitidine for Injection is reconstituted using refrigerated (2°C to 8°C, 36°F to 46°F) water for injection, the reconstituted product may be stored under refrigerated conditions (2°C to 8°C, 36°F to 46°F) for up to 30 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.

Azacitidine for Injection 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:** Azacitidine for Injection reconstituted with non-refrigerated water for injection for subcutaneous administration may be stored for up to 2 hours at 25°C (77°F) or for up to 12 hours between 2°C and 8°C (36°F and 46°F); when reconstituted with refrigerated (2°C to 8°C, 36°F to 46°F) water for injection, it may be stored for 30 hours between 2°C and 8°C (36°F and 46°F).

### **2.8 Instructions for Intravenous Administration**

Reconstitute the appropriate number of Azacitidine for Injection 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 Azacitidine for Injection solution to deliver the desired dose and inject into a 50 to 100 mL infusion bag of either 0.9% Sodium Chloride Injection or Lactated Ringer's Injection.

### **Intravenous Solution Incompatibility**

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

### **Intravenous Administration**

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

**Solution Stability:** Azacitidine for Injection 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**

Azacitidine for Injection is supplied as lyophilized powder in 100 mg single-dose vials.

## **4 CONTRAINDICATIONS**

### **4.1 Advanced Malignant Hepatic Tumors**

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

### **4.2 Hypersensitivity to Azacitidine**

Azacitidine for Injection is contraindicated in patients with a known hypersensitivity to azacitidine.

## **5 WARNINGS AND PRECAUTIONS**

### **5.1 Anemia, Neutropenia and Thrombocytopenia**

Azacitidine for Injection causes anemia, neutropenia and thrombocytopenia. Monitor complete blood counts frequently for response and/or toxicity, at a minimum, prior to each dosing cycle. After administration of the recommended dosage for the first cycle, adjust dosage for subsequent cycles based on nadir counts and hematologic response [*see Dosage and Administration (2.3)*].

### **5.2 Hepatic Toxicity in Patients with Severe Pre-existing Hepatic Impairment**

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 reported to experience progressive hepatic coma and death during azacitidine treatment, especially in such patients with baseline albumin less than 30 g/L. Azacitidine is contraindicated in patients with advanced malignant hepatic tumors [*see Contraindications (4.1)*].

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

### **5.3 Renal Toxicity**

Renal toxicity ranging from elevated serum creatinine to renal failure and death have been reported 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 less than 20 mEq/L in association with an alkaline urine and hypokalemia (serum potassium less than 3 mEq/L) developed in 5 patients with CML (an unapproved use) treated with azacitidine and etoposide. If unexplained reductions in serum bicarbonate less than 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 may be at increased risk for renal toxicity. Also, azacitidine and its metabolites are primarily excreted by the kidney. Therefore, these patients should be closely monitored for toxicity [*see Dosage and Administration (2.4, 2.5)*]. Patients with MDS and renal impairment were excluded from the clinical studies.

### **5.4 Embryo-Fetal Toxicity**

Based on findings from animal studies and its mechanism of action, Azacitidine for Injection can cause fetal harm when administered to a pregnant woman. In animal studies, azacitidine caused adverse developmental effects when administered to mice and rats at doses of 3 to 12 mg/m<sup>2</sup> and 6 mg/m<sup>2</sup> (approximately 4% to 16% and 8%) of the recommended human daily dose of 75 mg/m<sup>2</sup>, respectively. Advise pregnant women of the potential risk to the fetus.

Advise females of reproductive potential to use effective contraception during treatment with Azacitidine for Injection and for 1 week following the final dose. Advise males with female partners of reproductive potential

to use effective contraception during treatment with Azacitidine for Injection and for 3 months following the final dose [see *Use in Specific Populations (8.1 and 8.3) and Clinical Pharmacology (12.3)*].

## 6 ADVERSE REACTIONS

The following adverse reactions are described in other labeling sections:

- Anemia, neutropenia and thrombocytopenia [see *Warnings and Precautions (5.1)*]
- Hepatic Toxicity in Patients with Severe Pre-existing Hepatic Impairment [see *Warnings and Precautions (5.2)*]
- Renal Toxicity [see *Warnings and Precautions (5.3)*]

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

### **Adverse Reactions Most Frequently (Greater Than 2%) Resulting in Clinical Intervention (Subcutaneous or Intravenous Route):**

*Discontinuation:* leukopenia, thrombocytopenia, neutropenia.

*Dose Held:* leukopenia, neutropenia, thrombocytopenia, pyrexia, pneumonia, febrile neutropenia.

*Dose Reduced:* leukopenia, neutropenia, thrombocytopenia.

### **6.1 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 Azacitidine for Injection in 443 MDS patients from 4 clinical studies. Study 1 was a supportive-care controlled trial (subcutaneous administration), Studies 2 and 3 were single arm studies (one with subcutaneous administration and one with intravenous administration), and Study 4 was an international randomized trial (subcutaneous administration) [see *Clinical Studies (14)*].

In Studies 1, 2 and 3, a total of 268 patients were exposed to Azacitidine for Injection, including 116 exposed for 6 cycles (approximately 6 months) or more and 60 exposed for greater than 12 cycles (approximately one year). Azacitidine for Injection 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 intravenous 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>.

In Study 4, a total of 175 patients with higher-risk MDS (primarily RAEB and RAEB-T subtypes) were exposed to Azacitidine for Injection. 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 Azacitidine for Injection doses of 75 mg/m<sup>2</sup>.

Table 1 presents adverse reactions occurring in at least 5% of patients treated with Azacitidine for Injection (subcutaneous) in Studies 1 and 2. It is important to note that duration of exposure was longer for the Azacitidine for Injection-treated group than for the observation group: patients received Azacitidine for Injection 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 (Greater Than or Equal To 5.0% in All Subcutaneous Azacitidine for Injection-Treated Patients; Studies 1 and 2)**

| Body System<br>Adverse Reaction <sup>a</sup>                | Number (%) of Patients                                |                                    |
|---|---|------------------------------------|
|   | All Azacitidine for Injection <sup>b</sup><br>(N=220) | Observation <sup>c</sup><br>(N=92) |
| <b>Blood and lymphatic system disorders</b>                 |   |                                    |
| 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)                          |
| <b>Gastrointestinal disorders</b>                           |   |                                    |
| 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)                            |
| <b>General disorders and administration site conditions</b> |   |                                    |
| 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)                          |
| <b>Infections and infestations</b>                          |   |                                    |
| Nasopharyngitis   | 32 (14.5)   | 3 (3.3)                            |
| Pneumonia   | 24 (10.9)   | 5 (5.4)                            |
| Upper respiratory tract infection                           | 28 (12.7)   | 4 (4.3)                            |
| <b>Injury, poisoning, and procedural complications</b>      |   |                                    |
| Post procedural hemorrhage                                  | 13 (5.9)  | 1 (1.1)                            |
| <b>Metabolism and nutrition disorders</b>                   |   |                                    |
| Anorexia  | 45 (20.5)   | 6 (6.5)                            |
| <b>Musculoskeletal and connective tissue disorders</b>      |   |                                    |
| Arthralgia  | 49 (22.3)   | 3 (3.3)                            |
| Chest wall pain   | 11 (5.0)  | 0                                  |
| Myalgia   | 35 (15.9)   | 2 (2.2)                            |
| <b>Nervous system disorders</b>                             |   |                                    |
| Dizziness   | 41 (18.6)   | 5 (5.4)                            |
| Headache  | 48 (21.8)   | 10 (10.9)                          |
| <b>Psychiatric disorders</b>                                |   |                                    |
| Anxiety   | 29 (13.2)   | 3 (3.3)                            |
| Insomnia  | 24 (10.9)   | 4 (4.3)                            |
| <b>Respiratory, thoracic and mediastinal disorders</b>      |   |                                    |
| Dyspnea   | 64 (29.1)   | 11 (12.0)                          |



|   |           |           |
|---|-----------|-----------|
| <b>Skin and subcutaneous tissue disorders</b> |           |           |
| 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)   |
| <b>Vascular disorders</b>                     |           |           |
| Hematoma                                      | 19 (8.6)  | 0         |
| Hypotension                                   | 15 (6.8)  | 2 (2.2)   |
| Petechiae                                     | 52 (23.6) | 8 (8.7)   |

<sup>a</sup> Multiple terms of the same preferred terms for a patient are only counted once within each treatment group.

<sup>b</sup> Includes adverse reactions from all patients exposed to Azacitidine for Injection, including patients after crossing over from observations.

<sup>c</sup> Includes adverse reactions from observation period only; excludes any adverse events after crossover to Azacitidine for Injection.

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

**Table 2: Most Frequently Observed Adverse Reactions (Greater Than or Equal To 5.0% in the Azacitidine for Injection-Treated Patients and the Percentage with NCI CTC Grade 3/4 Reactions; Study 4)**

| Body System<br>Adverse Reactions <sup>a</sup>               | Number (%) of Patients                  |  |   |  |
|---|---|--|---|--|
|   | Any Grade                               |  | Grade 3/4                               |  |
|   | Azacitidine<br>for Injection<br>(N=175) | Best<br>Supportive<br>Care Only<br>(N=102) | Azacitidine<br>for Injection<br>(N=175) | Best<br>Supportive<br>Care Only<br>(N=102) |
| <b>Blood and lymphatic system disorders</b>                 |   |  |   |  |
| 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)                                  |
| <b>Gastrointestinal disorders</b>                           |   |  |   |  |
| 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  |
| <b>General disorders and administration site conditions</b> |   |  |   |  |
| 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)                                    |

|  |           |         |         |         |
|--|-----------|---------|---------|---------|
| <b>Infections and infestations</b>                     |           |         |         |         |
| 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       |
| <b>Investigations</b>                                  |           |         |         |         |
| Weight decreased                                       | 14 (8.0)  | 0       | 1 (0.6) | 0       |
| <b>Metabolism and nutrition disorders</b>              |           |         |         |         |
| Hypokalemia  | 11 (6.3)  | 3 (2.9) | 3 (1.7) | 3 (2.9) |
| <b>Nervous system disorders</b>                        |           |         |         |         |
| Lethargy   | 13 (7.4)  | 2 (2.0) | 0       | 1 (1.0) |
| <b>Psychiatric disorders</b>                           |           |         |         |         |
| Anxiety  | 9 (5.1)   | 1 (1.0) | 0       | 0       |
| Insomnia   | 15 (8.6)  | 3 (2.9) | 0       | 0       |
| <b>Renal and urinary disorders</b>                     |           |         |         |         |
| Hematuria  | 11 (6.3)  | 2 (2.0) | 4 (2.3) | 1 (1.0) |
| <b>Respiratory, thoracic and mediastinal disorders</b> |           |         |         |         |
| 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       |
| <b>Skin and subcutaneous tissue disorders</b>          |           |         |         |         |
| 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       |
| <b>Vascular disorders</b>                              |           |         |         |         |
| Hypertension   | 15 (8.6)  | 4 (3.9) | 2 (1.1) | 2 (2.0) |

<sup>a</sup> Multiple reports of the same preferred term from a patient were only counted once within each treatment.

In Studies 1, 2 and 4 with subcutaneous administration of Azacitidine for Injection, adverse reactions of neutropenia, thrombocytopenia, anemia, nausea, vomiting, diarrhea, constipation, and injection site erythema/reaction tended to increase in incidence with higher doses of Azacitidine for Injection. Adverse reactions that tended to be more pronounced during the first 1 to 2 cycles of subcutaneous 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 intravenous and subcutaneous studies. Adverse reactions that appeared to be specifically associated with the intravenous 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 subcutaneous or intravenous Azacitidine for Injection, the following serious adverse reactions occurring at a rate of less than 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.

## 6.2 Postmarketing Experience

The following adverse reactions have been identified during postmarketing use of Azacitidine for Injection. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Interstitial lung disease
- Tumor lysis syndrome
- Injection site necrosis
- Sweet's syndrome (acute febrile neutrophilic dermatosis)
- Necrotizing fasciitis (including fatal cases)

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

#### Risk Summary

Azacitidine for Injection, a nucleoside metabolic inhibitor, can cause fetal harm based on findings from animal studies and the drug's mechanism of action [*see Clinical Pharmacology (12.1)*]. There are no available data on Azacitidine for Injection use in pregnant women. Azacitidine caused adverse developmental effects, including CNS anomalies (exencephaly), limb and skeletal anomalies (missing ribs, oligodactily, and club foot), and other

fetal abnormality (cleft palate, cardiomyopathy, and hind paw hematoma) when administered during organogenesis in mice and rats at doses of 4% to 16% and 8% the recommended human daily dose of 75 mg/m<sup>2</sup>, respectively [see Data]. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage in the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

## Data

### *Animal Data*

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 to 12 mg/m<sup>2</sup> (approximately 4% to 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 to 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 to 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 to 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).

## **8.2 Lactation**

There is no information on the presence of Azacitidine for Injection or its metabolites in human milk, the effects on the breast-fed infant, or the effects on milk production. Because of the potential for serious adverse reactions in breastfed infants from Azacitidine for Injection, advise women not to breastfeed during treatment and for 24 hours after the final dose.

## **8.3 Females and Males of Reproductive Potential**

### Contraception

#### *Females*

Azacitidine for Injection can cause fetal harm. Advise females of reproductive potential to use effective contraception during treatment with Azacitidine for Injection and for 1 week after the final dose [see *Use in Specific Populations (8.1) and Clinical Pharmacology (12.3)*].

#### *Males*

Based on genotoxicity findings, advise males with female partners of reproductive potential to use effective contraception during treatment with Azacitidine for Injection and for 3 months after the final dose [see *Nonclinical Toxicology (13.1)*].

### Infertility

#### *Males*

Based on animal data, advise males that Azacitidine for Injection may impair fertility [*see Nonclinical Toxicology (13.1)*].

#### **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 less than 65 years of age and patients 65 years of age and older.

Elderly patients are more likely to have decreased renal function. Monitor renal function in these patients [*see Dosage and Administration (2.5) and Warnings and Precautions (5.3)*].

#### **8.6 Renal Impairment**

Severe renal impairment (CL<sub>cr</sub> less than 30 mL/min) has no major effect on the exposure of azacitidine after multiple subcutaneous administrations. Therefore, azacitidine can be administered to patients with renal impairment without Cycle 1 dose adjustment [*see Clinical Pharmacology (12.3)*].

#### **8.7 Gender**

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

#### **8.8 Race**

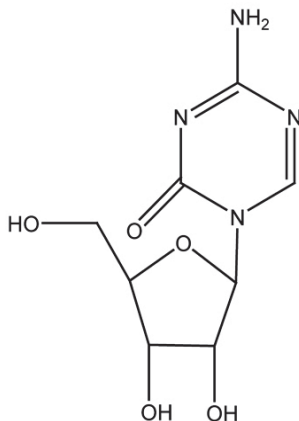
Greater than 90% of all patients in all trials were Caucasian. Therefore, no comparisons between Caucasians and non-Caucasians were possible.

### **10 OVERDOSAGE**

One case of overdose with Azacitidine for Injection was reported during clinical trials. A patient experienced diarrhea, nausea, and vomiting after receiving a single intravenous dose of approximately 290 mg/m<sup>2</sup>, 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 overdose, the patient should be monitored with appropriate blood counts and should receive supportive treatment, as necessary. There is no known specific antidote for Azacitidine for Injection overdose.

### **11 DESCRIPTION**

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 molecular formula is  $C_8H_{12}N_4O_5$ . The molecular weight is 244. Azacitidine is a white to almost white powder. 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. Each vial of Azacitidine for Injection contains 100 mg of azacitidine, 170 mg sucrose, monosodium phosphate monohydrate and disodium hydrogen phosphate, dihydrate as a sterile lyophilized powder.

## 12 CLINICAL PHARMACOLOGY

### 12.1 Mechanism of Action

Azacitidine for Injection is a pyrimidine nucleoside analog of cytidine. Azacitidine for Injection 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  $75 \text{ mg/m}^2$  subcutaneous dose and a single  $75 \text{ mg/m}^2$  intravenous dose.

#### Absorption

Azacitidine is rapidly absorbed after subcutaneous administration; the peak plasma azacitidine concentration of  $750 \pm 403 \text{ ng/ml}$  occurred in 0.5 hour. The bioavailability of subcutaneous azacitidine relative to intravenous azacitidine is approximately 89%, based on area under the curve.

#### Distribution

Mean volume of distribution following intravenous dosing is  $76 \pm 26 \text{ L}$ .

#### Metabolism

Mean apparent subcutaneous clearance is  $167 \pm 49 \text{ L/hour}$  and mean half-life after subcutaneous administration is  $41 \pm 8 \text{ minutes}$ . The AUC and  $C_{\text{max}}$  of subcutaneous administration of azacitidine in 21 patients with cancer

were approximately dose proportional within the 25 to 100 mg/m<sup>2</sup> dose range. Multiple dosing at the recommended dose-regimen does not result in drug accumulation.

### Excretion

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

### Specific Populations

In patients with cancer the pharmacokinetics of azacitidine in 6 patients with normal renal function (CL<sub>cr</sub> greater than 80 mL/min) and 6 patients with severe renal impairment (CL<sub>cr</sub> less than 30 mL/min) were compared following daily subcutaneous dosing (Days 1 through 5) at 75 mg/m<sup>2</sup>/day. Severe renal impairment increased azacitidine exposure by approximately 70% after single and 41% after multiple subcutaneous administrations. This increase in exposure was not correlated with an increase in adverse events. The exposure was similar to exposure in patients with normal renal function receiving 100 mg/m<sup>2</sup>. Therefore, a Cycle 1 dose modification is not recommended.

The effects of hepatic impairment, gender, age, or race on the pharmacokinetics of azacitidine have not been studied.

### Drug-Drug Interactions

No formal clinical drug interaction studies with azacitidine have 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.

An *in vitro* study with cultured human hepatocytes indicated that azacitidine at concentrations up to 100 μM (intravenous C<sub>max</sub> = 10.6 μM) does not cause any inhibition of CYP2B6 and CYP2C8. The potential of azacitidine to inhibit other 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**

### **13.1 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 to 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 3 times per week for 11 or 16 weeks at doses of 15 to 30 mg/m<sup>2</sup> (approximately 20 to 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.

## 14 CLINICAL STUDIES

### Myelodysplastic Syndromes (MDS)

Study 1 was a randomized, open-label, controlled trial carried out in 53 U.S. sites that compared the safety and efficacy of subcutaneous Azacitidine for Injection 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 (CMML). RA and RARS patients were included if they met one or more of the following criteria: required packed RBC transfusions; had platelet counts less than or equal to 50 x 10<sup>9</sup>/L; required platelet transfusions; or were neutropenic (ANC less than 1 x 10<sup>9</sup>/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 hematopoietic growth factors was prohibited. Baseline patient and disease characteristics are summarized in Table 3; the 2 groups were similar.

Azacitidine for Injection was administered at a subcutaneous dose of 75 mg/m<sup>2</sup> daily for 7 days every 4 weeks. The dose was increased to 100 mg/m<sup>2</sup> 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 Azacitidine for Injection 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 Azacitidine for Injection treatment.

**Table 3. Baseline Demographics and Disease Characteristics**

|                    | Azacitidine for Injection<br>(N=99) | Observation<br>(N=92) |
|--------------------|-------------------------------------|-----------------------|
| <b>Gender (n%)</b> |                                     |                       |
| Male               | 72 (72.7)                           | 60 (65.2)             |



|   |              |              |
|---|--------------|--------------|
| Female  | 27 (27.3)    | 32 (34.8)    |
| <b>Race (n%)</b>  |              |              |
| 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)      |
| <b>Age (years)</b>  |              |              |
| N   | 99           | 91           |
| Mean ± SD   | 67.3 ± 10.39 | 68.0 ± 10.23 |
| Range   | 31 to 92     | 35 to 88     |
| <b>Adjudicated MDS diagnosis at study entry (n%)</b>                |              |              |
| 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)      |
| <b>Transfusion product used in 3 months before study entry (n%)</b> |              |              |
| 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 |
|--|-------------------------|---|---|------|--------|-------|
| <b>Complete Response (CR), duration ≥4 weeks</b> | <b>Marrow</b>           | <5% blasts  |   |      |        |       |
|  | <b>Peripheral Blood</b> | Normal CBC if abnormal at baseline<br>Absence of blasts in the peripheral circulation   |   |      |        |       |
| <b>Partial Response (PR), duration ≥4 weeks</b>  | <b>Marrow</b>           | No marrow requirements  | ≥50% decrease in blasts<br>Improvement of marrow dyspoiesis |      |        |       |
|  | <b>Peripheral Blood</b> | ≥50% restoration in the deficit from normal levels of baseline white cells, hemoglobin and platelets if abnormal at baseline<br><br>No blasts in the peripheral circulation<br><br>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 Azacitidine for Injection-treated patients without AML (16.2% for all Azacitidine for Injection 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 Azacitidine for Injection 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 5<sup>th</sup> 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**

|                 | <b>Azacitidine for Injection<br/>(N=89)</b> | <b>Observation Before Crossover<br/>(N=83)</b> |                |
|-----------------|---|--|----------------|
| <b>Response</b> | <b>n (%)</b>                                | <b>n (%)</b>                                   | <b>P value</b> |
| 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 Azacitidine for Injection 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 Azacitidine for Injection 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 Azacitidine for Injection 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. Azacitidine for Injection 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 Azacitidine for Injection-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.

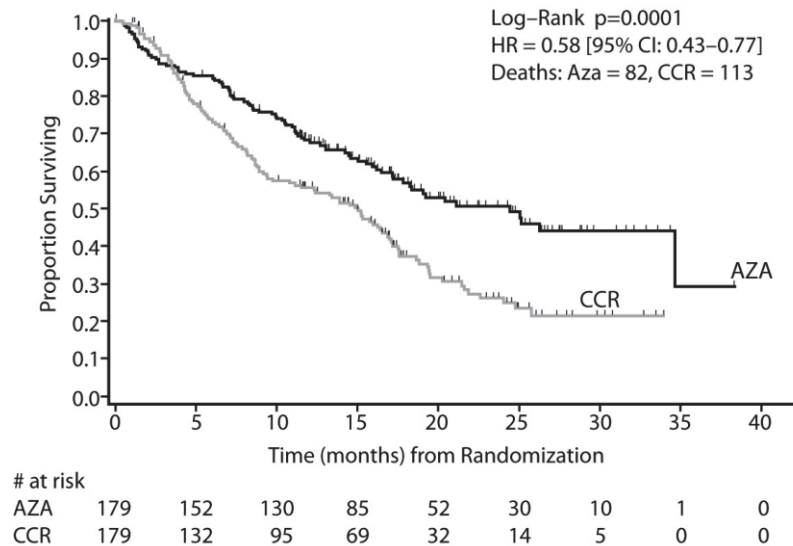
The azacitidine and CCR groups were comparable for baseline parameters. The median age of patients was 69 years (range was 38 to 88 years), 98% were Caucasian, and 70% were male. At baseline, 95% of the patients were higher risk by FAB classification: RAEB (58%), RAEB-T (34%), and CMMoL (3%). By IPSS 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<sup>2</sup> 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)**



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 <sup>1</sup> | 50/111 (45.0%)<br><br>(95% CI: 35.6%, 54.8%) | 13/114 (11.4%)<br><br>(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%)<br><br>(95% CI: 7.3%, 25.4%)   | 28/65 (43.1%)<br><br>(95% CI: 30.9%, 56.0%) |

<sup>1</sup> 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.

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Otherwise, the patient was considered transfusion dependent.

## 15 REFERENCES

1. “OSHA Hazardous Drugs.” OSHA. <http://www.osha.gov/SLTC/hazardousdrugs/index.html>

## 16 HOW SUPPLIED/STORAGE AND HANDLING

Azacitidine for Injection is supplied as a lyophilized powder in 100 mg single-dose vials packaged in cartons of 1 vial (NDC 0591-2897-49).

### Storage

Store unconstituted vials at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

Discard unused portion.

### Handling and Disposal

Azacitidine for Injection is a cytotoxic drug. Follow applicable special handling and disposal procedures.<sup>1</sup>

**Sterile, Nonpyrogenic, Preservative-free.**

**This vial stopper is not made with natural rubber latex.**

## 17 PATIENT COUNSELING INFORMATION

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

### Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to a fetus [see *Warnings and Precautions (5.4) and Use in Specific Populations (8.1)*].

Advise females of reproductive potential to use effective contraception during treatment with Azacitidine for Injection and for one week after the final dose [see *Use in Specific Populations (8.3)*].

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with Azacitidine for Injection and for 3 months after the final dose [see *Use in Specific Populations (8.3)*].

### Lactation

Advise women not to breastfeed during treatment with Azacitidine for Injection and for 24 hours after the final dose [see *Use in Specific Populations (8.2)*].

### Infertility

Advise males of the potential for reduced fertility from Azacitidine for Injection [see *Use in Specific Populations (8.3) and Nonclinical Toxicology (13.1)*].

Manufactured by:  
Sindan Pharma SRL  
11 Ion Mihalache Blvd.  
Bucharest 1, Romania 011171

Distributed by:  
Actavis Pharma, Inc.

Parsippany, NJ 07054 USA

Revised – April 2016





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Each vial contains:  
 100 mg of azacitidine,  
 170 mg sucrose,  
 monosodium phosphate  
 monohydrate and  
 disodium hydrogen  
 phosphate, dihydrate.

Store unconstituted  
 vials at 25°C (77°F);  
 excursions permitted  
 between 15° to 30°C  
 (59° to 86°F) [see USP  
 Controlled Room  
 Temperature].

Usual Dosage: See  
 prescribing information.

**Actavis**

Made in Romania  
 Dist. by: Actavis Pharma, Inc  
 Rev. 04/16

NDC 0591-2897-49

**Azacitidine for Injection**

**100 mg/vial** Lyophilized Powder

For Subcutaneous Use and Intravenous  
 Infusion After Reconstitution

Sterile, Nonpyrogenic, Preservative-free

Single-Dose Vial

Discard Unused Portion

0000 PS 00

**Cytotoxic Agent**

BATCH:  
 EXP:



(b) (4)

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/s/  
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ANN T FARRELL  
04/29/2016