

## Approval Summary: Azacitidine for Treatment of Myelodysplastic Syndrome Subtypes

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**Abstract Purpose:** This article summarizes data submitted to the U.S. Food and Drug Administration for marketing approval of azacitidine as injectable suspension (Vidaza, Pharmion Corporation, Boulder, CO) for treatment of patients with myelodysplastic syndrome.

**Experimental Design:** In one phase 3 controlled trial, 191 study subjects were randomized to treatment with azacitidine or to observation; an additional 120 patients were treated with azacitidine in two phase 2 single arm studies. The primary efficacy end point was the overall response rate, defined as complete or partial normalization of peripheral blood counts and bone marrow blast percentages for at least 4 weeks.

**Results:** In the controlled trial, the overall response rate was 15.7% in the azacitidine treatment group; there were no responders in the observation group ( $P < 0.0001$ ). Response rates were similar in the two single arm studies. During response patients stopped being red cell or platelet transfusion dependent. Median duration of responses was at least 9 months. An additional 19% of azacitidine-treated patients had less than partial responses, most becoming transfusion independent. The most common adverse events attributed to azacitidine were gastrointestinal, hematologic, local (injection site), and constitutional. There were no azacitidine-related deaths.

**Conclusions:** On May 19, 2004 the U.S. Food and Drug Administration approved azacitidine as injectable suspension for treatment of patients with the following myelodysplastic syndrome subtypes: refractory anemia or refractory anemia with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia. Full prescribing information is available at <http://www.fda.gov/cder/foi/label/2004/050794lbl.pdf>. Azacitidine is the first agent approved for treatment of myelodysplastic syndrome.

Several chronic diseases of bone marrow dysfunction, characterized by decreased counts of one or more blood cell types and/or an increase in bone marrow blasts, are grouped into an entity called myelodysplastic syndrome (MDS). The original French-American-British MDS classification (1) comprises five disease entities: refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess blasts (RAEB), RAEB in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMML). The differences between RAEB, RAEB-T, and acute myelogenous leukemia (AML) are based on marrow blast percentages; hence, it is not unusual for hematopathologists and laboratories to differ in classifying patients. The original French-American-British classification was used in the studies described in this application. Subsequently published MDS classifications include WHO (2), International Prognostic Scoring System (3), and International Working Group (4).

Disease progression in MDS patients is characterized by cytopenias, infections, bleeding, dependency on packed RBC and platelet transfusions, and development of AML. Prior to approval of azacitidine, the mainstay of therapy was supportive care. Therapy with high-dose cytotoxic agents has generally yielded disappointing results, and bone marrow or hematopoietic stem cell transplantation is not appropriate for the majority of MDS patients who are over 60 years of age (5).

A different form of therapy for MDS involves the use of agents that promote cell differentiation, such as azacitidine, an analogue of cytidine. Azacitidine is phosphorylated by a series of kinases to azacitidine triphosphate, which is incorporated into RNA, disrupting RNA metabolism and protein synthesis. Azacitidine diphosphate is reduced by ribonucleotide reductase to 5-aza-2'-deoxycytidine diphosphate, which is phosphorylated to triphosphate and incorporated into DNA. There it binds stoichiometrically DNA methyltransferases and causes hypomethylation of replicating DNA (6, 7).

DNA hypermethylation at the CpG islands is thought to accompany neoplastic transformation and silencing of a number of tumor suppressor genes. Azacitidine may act as an inducer of cell differentiation by causing demethylation and reexpression of genes silenced by hypermethylation (8). The discovery of

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hypermethylation of the  $p15^{INK4B}$  gene in MDS (9, 10) suggested that azacitidine may be effective in the treatment of MDS.

Azacitidine is also a cytotoxic agent in proliferating cells, but the concentration of azacitidine required for maximum inhibition of DNA methylation *in vitro* does not suppress synthesis of replicating DNA (11).

### Regulatory history

The original Investigational New Drug application for azacitidine was submitted by the National Cancer Institute in 1971 for various antineoplastic indications. By 1976 more than 800 patients with AML, chronic myelogenous leukemia, and various solid tumors had been treated with a variety of azacitidine regimens (12). Patients with severe  $\beta$ -thalassemia or with homozygous sickle cell disease treated with lower doses of azacitidine showed an increased fetal hemoglobin synthesis (13, 14), suggesting an effect of azacitidine on cell differentiation.

Three multicenter Cancer and Leukemia Group B (CALGB) trials (15–17) and seven single center trials (18–24) carried out between 1985 and 2002 documented azacitidine activity in MDS patients. Pharmion Corporation submitted a New Drug Application based on the data of the three CALGB trials.

### Chemistry

The active ingredient of Vidaza (Pharmion Corporation, Boulder, CO) is azacitidine (5-azacitidine), an analogue of cytidine. The chemical structures of azacitidine and of cytidine are shown in Fig. 1. Azacitidine differs from cytidine in containing a nitrogen atom in the 5 position of the heterocyclic ring instead of a carbon atom. The chemical name of azacitidine is 4-amino-1- $\beta$ -D-ribofuranosyl-s-triazin-2(1H)-one, the empirical formula of azacitidine is  $C_8H_{12}N_4O_5$ , and the molecular weight is 244.

Azacitidine is a white to off-white solid that is stable at 25°C, not light sensitive, sparingly soluble in water, and unstable when reconstituted in aqueous solution. Hydrolytic degradation at 25°C to 30°C results in a 21% to 36% loss over 8 hours; at 5°C the loss is 2% to 3% over 8 hours.

### Toxicology

Acute and repeated dose toxicology studies have identified bone marrow, liver, kidney, and lymphoid tissues as the target organs and tissues. Mortality was due to bone marrow failure.

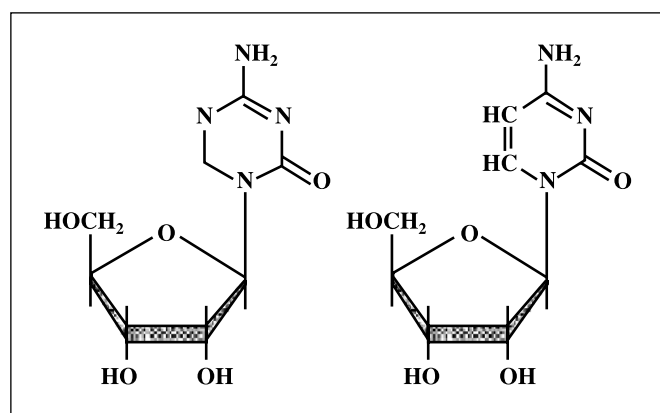


Fig. 1. Molecular structures of azacitidine (left) and cytidine (right).

Azacitidine was found to be mutagenic (25), clastogenic (25), and carcinogenic (26). Azacitidine decreased male fertility (27) and was embryotoxic when females were dosed during gestation or treated males were mated to untreated females (27, 28). Teratogenicity induced by azacitidine included central nervous system, limb, and skeletal anomalies and other fetal abnormalities (29).

### Clinical pharmacology

Azacitidine is rapidly absorbed following s.c. administration. Maximum plasma concentration is attained in about 30 minutes. Azacitidine is widely distributed, and is rapidly eliminated, with a mean plasma half-life of about 41 minutes.

Metabolism of azacitidine involves deamination by cytidine deaminase followed by opening of the ring structure (30). Azacitidine and its metabolites are primarily excreted by the kidneys.

The effects of intrinsic factors such as age, gender, race, renal impairment, or hepatic impairment on the pharmacokinetics of azacitidine have not been studied. *In vivo* drug-drug interaction studies have not been conducted. *In vitro* studies in cultured human hepatocytes indicate that azacitidine at a clinically relevant concentrations is not an inducer of CYP 1A2, 2C19, or 3A4/5.<sup>1</sup>

### Clinical trials

**Study design.** The controlled trial (CALGB 9221) was a multicenter, randomized, open-label trial designed to compare the safety and efficacy of s.c. administered azacitidine (azacitidine group) with supportive care (observation group) in patients with any of the five subtypes of MDS. RA and RARS patients were included if they required packed RBC transfusions for  $\geq 3$  months for symptomatic anemia, had platelet counts of  $\leq 50 \times 10^9/L$  or significant hemorrhage, required platelet transfusions, or were neutropenic (absolute neutrophil count  $< 1 \times 10^9/L$ ) with infections requiring treatment with antibiotics. Patients randomized to the observation group were allowed to cross over to azacitidine treatment after two to four cycles of therapy if they met prespecified criteria of disease progression. Blocked randomization included stratification by the five MDS subtypes. Patients with hepatic or renal impairment were excluded from the trials.

The two supporting studies were open-label, multicenter single arm studies, one treating patients with azacitidine administered s.c. (CALGB 8921), the other i.v. (CALGB 8421).

**Treatment.** The starting azacitidine dose, administered s.c. or i.v., was 75 mg/m<sup>2</sup> for 7 days every 28 days. The dose was to be decreased for hematologic toxicity and renal function abnormalities, and increased for lack of efficacy in absence of toxicity. Patients with no response after four azacitidine treatment cycles were to be taken off the study.

**Efficacy end points.** Overall response rate [complete response (CR) + partial response (PR)] was the primary efficacy end point. CR was defined as complete normalization of blood cell counts and bone marrow blast percentages for at least 4 weeks. PR was defined as  $\geq 50\%$  restoration in the deficit from normal levels of baseline blood cell counts, absence of blasts in peripheral blood,

<sup>1</sup> Pharmion Corporation, unpublished data.

and  $\geq 50\%$  decrease in bone marrow blasts from baseline (in RAEB, RAEB-T, and CMML patients) for at least 4 weeks.

Secondary efficacy end points were time-to-event analyses of death, disease progression, relapse, transformation to AML, and transformation to AML or death. Changes in RBC and platelet transfusions, hemoglobin concentrations, WBC, absolute neutrophil, and platelet counts, rates of infections requiring antibiotic therapy, hemorrhage rates, and percentages of marrow blasts were also assessed.

**Results.** In the controlled trial a total of 191 subjects were randomized at 53 sites, 99 to the azacitidine treatment arm, and 92 to the observation arm. Subjects in the two arms were well matched by age, gender, race, height, weight, performance status, MDS subtypes, number of patients adjudicated to have AML, and transfusion history. If the baseline diagnosis of AML was made either by the site or by the CALGB central hematopathologist, the diagnosis of AML was assigned to the subject.

Fifty one (55%) of the observation arm subjects crossed over to the azacitidine treatment arm. Thus, 150 of the 191 subjects were treated with azacitidine. About one half received  $<75$  mg/m<sup>2</sup>/d for 7 days every 28-day cycle for a mean duration of about 17 months, and about one half received  $\geq 75$  mg/m<sup>2</sup>/d for 7 days every cycle for a mean duration of about 7 months. Nineteen patients received 100 mg/m<sup>2</sup>/d; no one received a higher dose in this trial.

Study completion information and follow-up status after study completion were available for all 191 subjects. A common reason for withdrawal from both treatment arms was the development of AML, which was more common in the observation arm (44% of patients) than in the azacitidine treatment arm (14% of patients randomized to azacitidine and 12% of patients who crossed over to azacitidine after being randomized to the observation arm). Another common reason for withdrawal from the trial in the azacitidine arm (20% of patients) was no response after four cycles of azacitidine therapy.

The overall response rate (CR + PR) for subjects randomized to azacitidine was 16.2%; there were no responses among subjects randomized to observation (Table 1). The difference was statistically significant ( $P < 0.0001$ ). The overall response rate in subjects who crossed over to azacitidine treatment was 11.8%; there were no responses in subjects who remained in the observation arm without crossing over. The overall response rate in all azacitidine-treated subjects was 14.7%.

The response rate was the same (14.7%) after exclusion of subjects who were adjudicated to have had a diagnosis of AML at study entry (there were 10 such subjects in the azacitidine arm and 9 in the observation arm). Thirty-four patients randomized to the azacitidine treatment arm and 32 patients randomized to the observation arm had major protocol violations, which consisted mainly of receiving systemic

corticosteroids before transfusions or of hematopoietic growth factors before study entry. After exclusion of these subjects, the overall response rate was 20.0%.

Response rates to azacitidine treatment were similar in the two single-arm studies. CALGB 8921 study enrolled 72 subjects with RAEB (33 subjects), RAEB-T (29 subjects), and CMML (9 subjects) in 30 centers. Subject demographics and performance status were similar to those in the controlled trial. Seventeen subjects were found to have had AML at study entry. The overall response rate in the intent-to-treat population was 13.9%, 12.7% after exclusion of subjects with AML, and 15.4% after exclusion of subjects with AML and of subjects with protocol violations.

CALGB 8421 study enrolled 48 subjects with RAEB (23 subjects), RAEB-T (24 subjects), and AML (1 subject). Subject demographics were similar to those in the controlled trial. The overall response rate in the intent-to-treat population was 18.8%. Exclusion of the one subject with baseline diagnosis of AML did not change the response rate (19.1%). Exclusion of subjects with AML and of subjects with protocol violations resulted in a response rate of 20.0%.

In summary (Table 2), the response rate among all 270 patients treated with azacitidine in the three trials was 15.2%. The response rate among 238 patients with MDS was 15.1%.

Response rates were similar in subjects with all MDS subtypes and with AML (Table 3). Response rates were similar in both genders and across all age groups. There were 26 responders among 183 males (14.2%) and 15 responders among 87 females (17.2%). There were 15 responders among 100 patients less than 65 years of age (15.0%), 19 responders among 115 patients of ages 65 to 74 years (16.5%), and 7 responders among 55 patients of ages 75 years or more (12.7%). Racial or ethnic differences in response rates could not be detected because  $>95\%$  of subjects were white. Response rates were not related to azacitidine dose.

CRs generally occurred after 5 to 15 cycles of therapy. PRs occurred after 1 to 21 cycles of therapy. During the period of CR or PR, patients who had been dependent on packed RBC and/or platelet transfusions became transfusion independent. Responses were generally long lasting; 75% of the responding patients were still in response at the completion of all three studies. In the controlled trial, the median duration of response was at least 330 days and the mean duration was at least 512 days. In the two single arm trials, the median duration was at least 430 days in CALGB 8921 study and at least 281 days in CALGB 8421 study, with mean duration of at least 810 days in CALGB 8921 and of at least 398 days in CALGB 8421.

In addition to patients with CR or PR, about 19% of azacitidine-treated patients in the three trials had lesser responses termed "improvement" (defined as  $\geq 50\%$  restoration

**Table 1.** Response rates to azacitidine in the controlled trial\*

Response	Azacitidine	Observation before crossover	Observation without crossover	Azacitidine after crossover
CR + PR	16/99 (16.2%)	0/92 (0%)	0/41 (0%)	6/51 (11.8%)
CR	6 (6.1%)	0	0	3 (5.9%)
PR	10 (10.1%)	0	0	3 (5.9%)

\* All randomized patients (intent-to-treat population).

**Table 2.** Response rates to azacitidine in all three studies\*

Response	CALGB 9221	CALGB 8921	CALGB 8421	Total
CR + PR	22/150 (14.7%)	10/72 (13.9%)	9/48 (18.8%)	41/270 (15.2%)
CR	9	4	3	16 (5.9%)
PR	13	6	6	25 (9.3%)

\*All randomized patients (intent-to-treat population).

in the deficit from normal in one or more peripheral blood cell lines or a  $\geq 50\%$  decrease in RBC or platelet transfusion requirements). About two thirds of transfusion-dependent patients became transfusion independent with improvement response. The median duration of improvement responses was 195 days. In the observation arm, 6% of patients met the criteria for improvement as a result of increases in platelet or neutrophil counts. All of these patients were anemic, but none of them had an increase in hemoglobin values.

Azacitidine treatment could not be shown to result in a survival benefit or in delay in progression to AML because of the crossover of observation arm patients to azacitidine treatment.

**Safety.** In the controlled trial, >95% patients in both groups reported treatment-associated adverse events. Azacitidine-treated subjects reported more frequently than observation arm subjects gastrointestinal events (nausea, vomiting, diarrhea, constipation, and anorexia), neutropenia, febrile neutropenia, thrombocytopenia, injection site events, arthralgia, dizziness, dyspnea, cough, and myalgia. Serious adverse events occurred more frequently in azacitidine-treated patients (60%) than in observation patients (36%). Serious adverse events most commonly resulting in hospitalization were thrombocytopenia, febrile neutropenia, fever, and pneumonia. There were no deaths attributed to azacitidine treatment. During the study periods, half of the deaths in the three trials were probably related to MDS and the other half were unrelated to MDS.

The most common reasons for azacitidine discontinuation, dose reduction, or therapy interruption were leukopenia, neutropenia, and thrombocytopenia. Patients who developed CR or PR first had further decreases in hematologic parameters. Most patients in both treatment arms received packed RBC and/or platelet transfusions and medications to treat adverse events. The frequency of adverse events decreased after the first two cycles of azacitidine therapy.

Liver function abnormalities, which coincided with intercurrent illnesses including hepatobiliary disorders, occurred in about 16% of azacitidine-treated subjects and in 8% of observation subjects. Three patients in the azacitidine arm developed hepatic impairment; two of them had been previously diagnosed with liver cirrhosis. Renal failure developed in five azacitidine arm patients and in one observation arm patient, in settings of sepsis, hypotension, heart failure, and diabetes mellitus.

Adverse events occurred at about the same frequency in males and females and in all age groups.

## Discussion

The three CALGB trials were the largest trials of azacitidine in MDS to date, and the effects of azacitidine on CR + PR and transfusion requirements were reproducible. Although only one trial had a control group, it is clear that spontaneous remissions do not occur in MDS, so that the single arm studies are convincing with respect to response. Other single-arm trials of azacitidine in MDS with similar or higher efficacy have been reported in the literature (18–24). The clinical benefit of response to azacitidine treatment was shown in long-lasting increases in peripheral blood cell counts, which made transfusions unnecessary. Decreased bone marrow blast percentages were similarly long lasting. However, improvement in survival or delay in progression to AML could not be shown.

Azacitidine seems to be a relatively safe drug for a premalignant or malignant condition such as MDS, although adverse events were common. The most common adverse events were gastrointestinal, which were prevented or controlled with concomitant medications, and hematologic, which exacerbated the hematopoietic cytopenias characteristic of MDS. The latter finding is consistent with all published

**Table 3.** Response rates to azacitidine in all three trials by in MDS subtypes and in AML\*

MDS subtypes and AML	CALGB 9221	CALGB 8921	CALGB 8421	Total
RA	7/35	—	—	7/35 (20.0%)
RARS	1/8	—	—	1/8 (12.5%)
RAEB	8/58	4/26	4/23	16/107 (15.5%)
RAEB-T	2/23	2/20	5/24	9/67 (13.4%)
CMML	2/10	1/9	—	3/19 (15.8%)
AML	2/16	3/17	0/1	5/34 (14.7%)

\*All randomized patients.

studies citing hematologic toxicity as dose limiting. No deaths were attributed to azacitidine in these studies. However, azacitidine was a possible or probable contributor to 21 deaths in cancer patients reported by National Cancer Institute. Most deaths were due to infections, neutropenia, and thrombocytopenia.

Hepatic and renal adverse events were rare, possibly because patients with hepatic or renal impairment were excluded from participation in these studies. Prior reports described hepatic coma developing in patients with hepatic metastases from solid tumors (12). Renal function abnormalities had been previously reported in patients treated with combination chemotherapy, some with preexisting renal impairment (12). Hence, caution is advisable in treating patients with hepatic or renal impairment.

The trial protocols specified that subjects should be dismissed from the trial if no response occurred after four cycles of therapy. Fifty of 270 patients (18.5%) in the azacitidine treatment groups in the three trials were discontinued for this reason. However, four cycles of therapy were too

few to conclude a lack of efficacy for some patients. CR or PR took longer time to develop.

The CALGB protocols also specified that patients who achieved a CR were to be withdrawn from the study after three further cycles. Most of the CR patients followed this instruction; however, some CR and most PR patients continued to receive azacitidine until they were withdrawn from the study for other reasons. The instructions in the label state that treatment may be continued as long as the patient continues to benefit.

In summary, On May 19, 2004 the U.S. Food and Drug Administration approved azacitidine as injectable suspension (Vidaza) for treatment of patients with the following MDS subtypes: RA or RARS (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), RAEB, RAEB-T, and CMML. Azacitidine is the first agent approved for treatment of myelodysplastic syndrome. Full prescribing information is available at <http://www.fda.gov/cder/foi/label/2004/050794lbl.pdf>.

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