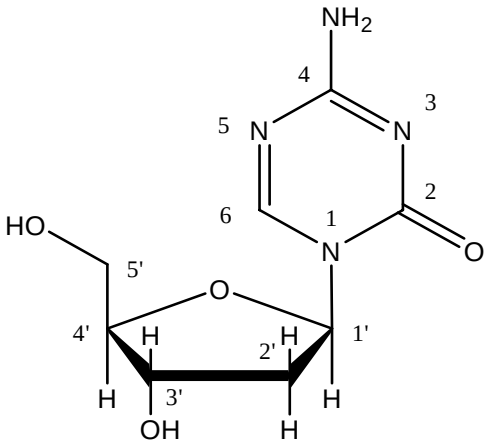
DACOGEN™ (DECITABINE) FOR INJECTION

DESCRIPTION

Dacogen™ (decitabine) for Injection contains decitabine (5-aza-2'-deoxycytydine), an analogue of the natural nucleoside 2'-deoxycytidine. Decitabine is a fine, white to almost white powder with the molecular formula of $C_8H_{12}N_4O_4$ and a molecular weight of 228.21. Its chemical name is 4-amino-1-(2-deoxy-β-D-erythro-pentofuranosyl)-1,3,5-triazin-2(1*H*)-one and it has the following structural formula:



Decitabine is slightly soluble in ethanol/water (50/50), methanol/water (50/50) and methanol; sparingly soluble in water and soluble in dimethylsulfoxide (DMSO).

Dacogen™ (decitabine) for Injection is a white to almost white sterile lyophilized powder supplied in a clear colorless glass vial. Each 20 mL, single dose, glass vial contains 50 mg decitabine, 68 mg monobasic potassium phosphate (potassium dihydrogen phosphate) and 11.6 mg sodium hydroxide.

CLINICAL PHARMACOLOGY

Mechanism of Action

Decitabine is believed to exert its antineoplastic effects after phosphorylation and direct incorporation into DNA and inhibition of DNA methyltransferase, causing hypomethylation of DNA and cellular differentiation or apoptosis. Decitabine inhibits DNA methylation *in vitro,* which is achieved at concentrations that do not cause major suppression of DNA synthesis. Decitabine-induced hypomethylation in neoplastic cells may restore normal function to genes that are critical for the control of cellular differentiation and proliferation. In rapidly dividing cells, the cytotoxicity of decitabine may also be attributed to the formation of covalent adducts between DNA methyltransferase and decitabine incorporated into DNA. Non-proliferating cells are relatively insensitive to decitabine.

Pharmacokinetics

No information is available on the pharmacokinetics of decitabine at the indicated dosage of 15 mg/m^2. Patients with advanced solid tumors received a 72-hour infusion of decitabine at 20 to 30 mg/m^2/day.

Decitabine pharmacokinetics were characterized by a biphasic disposition. The total body clearance (mean ± SD) was 124 ± 19 L/hr/m^2, and the terminal phase elimination half-life was 0.51 ± 0.31 hr. Plasma protein binding of decitabine is negligible (<1%).

The exact route of elimination and metabolic fate of decitabine is not known in humans. One of the pathways of elimination of decitabine appears to be deamination by cytidine deaminase found principally in the liver but also in granulocytes, intestinal epithelium and whole blood.

Special Populations

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

Drug-Drug Interactions

Drug interaction studies with decitabine have not been conducted. In vitro studies in human liver microsomes suggest that decitabine is unlikely to inhibit or induce cytochrome P450 enzymes. *In vitro* metabolism studies have suggested that decitabine is not a substrate for the human liver cytochrome P450 enzymes. As plasma protein binding of decitabine is negligible (<1%), interactions due to displacement of more highly protein bound drugs from plasma proteins are not expected.

CLINICAL STUDIES

Phase 3 Trial

A randomized open-label, multicenter, controlled trial evaluated 170 adult patients with myelodysplastic syndromes (MDS) meeting French-American-British (FAB) classification criteria and International Prognostic Scoring System (IPSS) High-Risk, Intermediate-2 and Intermediate-1 prognostic scores. Eighty-nine patients were randomized to Dacogen therapy plus supportive care (only 83 received Dacogen), and 81 to Supportive Care (SC) alone. Patients with Acute Myeloid Leukemia (AML) were not intended to be included. Of the 170 patients included in the study, independent review (adjudicated diagnosis) found that 12 patients (9 in the Dacogen arm and 3 in the SC arm) had the diagnosis of AML at baseline. Baseline demographics and other patient characteristics in the Intent-to-Treat (ITT) population were similar between the 2 groups, as shown in **Table 1**.

Table 1 Baseline Demographics and Other Patient Characteristics (ITT)

Demographic or Other Patient Characteristic	**Dacogen**	**Supportive Care**
	N=89	**N=81**
Age (years)		
Mean (±SD)	69±10	67±10
Median (IQR)	70 (65-76)	70 (62-74)
(Range: min-max)	(31-85)	(30-82)
Gender n (%)		
Male	59 (66)	57 (70)
Female	30 (34)	24 (30)
Race n (%)		
White	83 (93)	76 (94)
Black	4 (4)	2 (2)
Other	2 (2)	3 (4)
Weeks Since MDS Diagnosis		
Mean (±SD)	86±131	77±119
Median (IQR)	29 (10-87)	35 (7-98)
(Range: min-max)	(2-667)	(2-865)
Previous MDS Therapy n (%)		
Yes	27 (30)	19 (23)
No	62 (70)	62 (77)
RBC Transfusion Status n (%)		
Independent	23 (26)	27 (33)
Dependent	66 (74)	54 (67)
Platelet Transfusion Status n (%)		
Independent	69 (78)	62 (77)
Dependent	20 (22)	19 (23)
IPSS Classification n (%)		
Intermediate–1	28 (31)	24 (30)
Intermediate–2	38 (43)	36 (44)
High Risk	23 (26)	21 (26)

Table 1 Baseline Demographics and Other Patient Characteristics (Cont'd)

Demographic or Other Patient Characteristic	Dacogen	Supportive Care
FAB Classification n (%)	**N=89**	**N=81**
RA	12 (13)	12 (15)
RARS	7 (8)	4 (5)
RAEB	47 (53)	43 (53)
RAEB-t	17 (19)	14 (17)
CMML	6 (7)	8 (10)

Patients randomized to the Dacogen arm received Dacogen intravenously infused at a dose of 15 mg/m^2 over a 3-hour period, every 8 hours, for 3 consecutive days. This cycle was repeated every 6 weeks, depending on the patient's clinical response and toxicity. Supportive care consisted of blood and blood product transfusions, prophylactic antibiotics, and hematopoietic growth factors. Co-primary endpoints of the study were overall response rate (complete response + partial response) and time to AML or death. Responses were classified using the MDS International Working Group (IWG) criteria; patients were required to be RBC and platelet transfusion independent during the time of response. Response criteria are given in **Table 2**:

Table 2 Response Criteria for Phase 3 Trial*

Complete	**Bone**	**On repeat aspirates:**
Response (CR) ≥ 8 weeks	**Marrow**	• < 5% myeloblasts • No dysplastic changes
	Peripheral	**In all samples during response:**
	Blood	• Hgb > 11g/dL (no transfusions or erythropoietin) • ANC ≥ 1500/μL (no growth factor) • Platelets ≥ 100,000/μL (no thrombopoietic agent) • No blasts and no dysplasia
Partial	**Bone**	**On repeat aspirates:**
Response (PR) ≥ 8 weeks	**Marrow**	• ≥ 50% decrease in blasts over pretreatment values OR • Improvement to a less advanced MDS FAB classification
	Peripheral	**Same as for CR**
	Blood	

* Cheson BD, Bennett JM, et al. Report of an International Working Group to Standardize Response Criteria for MDS. *Blood*. 2000; 96:3671-3674.

The overall response rate (CR+PR) in the ITT population was 17% in Dacogen-treated patients and 0% in the SC group (p<0.001). (**See Table 3**) The overall response rate was 21% (12/56) in Dacogen-treated patients considered evaluable for response (i.e., those patients with pathologically confirmed MDS at baseline who received at least 2 cycles of treatment). The median duration of response (range) for patients who responded to Dacogen was 288 days (116-388) and median time to response (range) was 93 days (55-272). All but one of the Dacogen-treated patients who responded did so by the fourth cycle. Benefit was seen in an additional 13% of Dacogen-treated patients who had hematologic improvement, defined as a response less than PR lasting at least 8 weeks, compared to 7% of SC patients. Dacogen treatment did not significantly delay the median time to AML or death versus supportive care.

Table 3 Analysis of Response (ITT)

	Dacogen	**Supportive Care**
Parameter	**N=89**	**N=81**
Overall Response Rate (CR+PR) †	**15 (17%)****	**0 (0%)**
Complete Response (CR)	8 (9%)	0 (0%)
Partial Response (PR)	7 (8%)	0 (0%)
Duration of Response		
Median time to (CR+PR) response Days (range)	93 (55-272)	NA
Median Duration of (CR+PR) response Days (range)	288 (116-388)	NA

**** p-value <0.001 from two-sided Fisher's Exact Test comparing Dacogen vs. Supportive Care.**

†In the co-primary endpoint model, a p-value of ≤ 0.024 was required to achieve statistical significance.

All patients with a CR or PR were RBC and platelet transfusion independent in the absence of growth factors.

Responses occurred in patients with an adjudicated baseline diagnosis of AML.

Phase 2 Studies

Two additional open-label, single-arm, multicenter studies in Europe were conducted to evaluate the safety and efficacy of Dacogen in MDS patients with any of the FAB subtypes. Dacogen was intravenously infused at a dose of 15 mg/m^2 over a 4-hour period, every 8 hours, on days 1, 2 and 3 of week 1 every 6 weeks (1 cycle). The results of the Phase 2 studies were consistent with the results of the Phase 3 trial with overall response rates of 26% (N=66) and 24% (N=98).

INDICATIONS AND USAGE

Dacogen is indicated for treatment of patients with myelodysplastic syndromes (MDS) including previously treated and untreated, *de novo* and secondary MDS of all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups.

CONTRAINDICATIONS

Dacogen is contraindicated in patients with a known hypersensitivity to decitabine.

WARNINGS

Pregnancy – Teratogenic effects: Pregnancy Category D

Dacogen may cause fetal harm when administered to a pregnant woman. The developmental toxicity of decitabine was examined in mice exposed to single IP (intraperitoneal) injections (0, 0.9 and 3.0 mg/m^2, approximately 2% and 7% of the recommended daily clinical dose, respectively) over gestation days 8, 9, 10 or 11. No maternal toxicity was observed but reduced fetal survival was observed after treatment at 3 mg/m^2 and decreased fetal weight was observed at both dose levels. The 3 mg/m^2 dose elicited characteristic fetal defects for each treatment day, including supernumerary ribs (both dose levels), fused vertebrae and ribs, cleft palate, vertebral defects, hind-limb defects and digital defects of fore- and hind-limbs. In rats given a single IP injection of 2.4, 3.6 or 6 mg/m^2 (approximately 5, 8 or 13% the daily recommended clinical dose, respectively) on gestation days 9-12, no maternal toxicity was observed. No live fetuses were seen at any dose when decitabine was injected on gestation day 9. A significant decrease in fetal survival and reduced fetal weight at doses greater than 3.6 mg/m^2 was seen when decitabine was given on gestation day 10. Increased incidences of vertebral and rib anomalies were seen at all dose levels, and induction of exophthalmia, exencephaly, and cleft palate were observed at 6.0 mg/m^2. Increased incidence of foredigit defects was seen in fetuses at doses greater than 3.6 mg/m^2. Reduced size and ossification of long bones of the fore-limb and hind-limb were noted at 6.0 mg/m^2.

There are no adequate and well-controlled studies in pregnant women using Dacogen. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Dacogen. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Use in Males

Men should be advised not to father a child while receiving treatment with Dacogen. and for 2 months afterwards. (See **PRECAUTIONS**: **Carcinogenesis, Mutagenesis, and Impairment of Fertility** for discussion of pre-mating effects of decitabine exposure on male fertility and embryonic viability.)

PRECAUTIONS

General

Treatment with Dacogen is associated with neutropenia and thrombocytopenia. Complete blood and platelet 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 adjusted as described in **DOSAGE AND ADMINISTRATION**. Clinicians should consider the need for early institution of growth factors and/or antimicrobial agents for the prevention or treatment of infections in patients with MDS. Myelosuppression and worsening neutropenia may occur more frequently in the first or second treatment cycles, and may not necessarily indicate progression of underlying MDS.

There are no data on the use of Dacogen in patients with renal or hepatic dysfunction; therefore, Dacogen should be used with caution in these patients. While metabolism is extensive, the cytochrome P450 system does not appear to be involved. In clinical trials, Dacogen was not administered to patients with serum creatinine > 2.0 mg/dL, transaminase greater than 2 times normal, or serum bilirubin > 1.5 mg/dL.

Information for Patients

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

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

Men should be advised not to father a child while receiving treatment with Dacogen, and for 2 months afterwards.

Laboratory Tests

Complete blood counts and platelet 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 treatment.

Drug-Drug Interactions

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

Carcinogenesis, Mutagenesis, and Impairment of Fertility

No formal carcinogenicity evaluation of decitabine has been performed.

The mutagenic potential of decitabine was tested in several *in vitro* and *in vivo* systems. Decitabine increased mutation frequency in L5178Y mouse lymphoma cells, and mutations were produced in an *Escherichia coli lac-I* transgene in colonic DNA of decitabine-treated mice. Decitabine caused chromosomal rearrangements in larvae of fruit flies.

The effect of decitabine on postnatal development and reproductive capacity was evaluated in mice administered a single 3 mg/m^2 IP injection (approximately 7% the recommended daily clinical dose) on day 10 of gestation. Body weights of males and females exposed *in utero* to decitabine were significantly reduced relative to controls at all postnatal time points. No consistent effect on fertility was seen when female mice exposed *in utero* were mated to untreated males. Untreated females mated to males exposed *in utero* showed decreased fertility at 3 and 5 months of age (36% and 0% pregnancy rate, respectively). In male mice given IP injections of 0.15, 0.3 or 0.45 mg/m^2 decitabine (approximately 0.3% to 1% the recommended clinical dose) 3 times a week for 7 weeks, decitabine did not affect survival, body weight gain or hematological measures (hemoglobin and WBC counts). Testes weights were reduced, abnormal histology was observed and significant decreases in sperm number were found at doses $\geq$ 0.3 mg/m^2. In females mated to males dosed with $\geq$ 0.3 mg/m^2 decitabine, pregnancy rate was reduced and preimplantation loss was significantly increased.

Pregnancy

Teratogenic Effects: Category D. See WARNINGS section

Nursing Mothers:

It is not known whether decitabine or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions from Dacogen in nursing infants, a decision should be made whether to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use:

The safety and effectiveness in pediatric patients have not been established.

Geriatric Use:

Of the total number of patients exposed to Dacogen in the phase 3 study, 61 of 83 patients were age 65 and over, while 21 of 83 patients were age 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has

not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Most Commonly Occurring Adverse Reactions: neutropenia, thrombocytopenia, anemia, fatigue, pyrexia, nausea, cough, petechiae, constipation, diarrhea, and hyperglycemia.

Adverse Reactions Most Frequently (≥ 1%) Resulting in Clinical Intervention in the Phase 3 Trial in the Dacogen Arm:

Discontinuation: thrombocytopenia, neutropenia, pneumonia, Mycobacterium avium complex infection, cardio-respiratory arrest, increased blood bilirubin, intracranial hemorrhage, abnormal liver function tests.

Dose Delayed: neutropenia, pulmonary edema, atrial fibrillation, central line infection, febrile neutropenia.

Dose Reduced: neutropenia, thrombocytopenia, anemia, lethargy, edema, tachycardia, depression, pharyngitis.

Discussion of Adverse Reactions Information

Dacogen was studied in 2 single-arm Phase 2 studies (N = 66, N = 98) and 1 controlled Phase 3 (Supportive Care) study (N = 83 exposed to Dacogen). The data described below reflect exposure to Dacogen in 83 patients in the Phase 3 MDS trial. In the Phase 3 trial, patients received 15 mg/m^2 intravenously every 8 hours for 3 days every 6 weeks. The median number of Dacogen cycles was 3 (range 0 to 9).

Table 4 presents all adverse events regardless of causality occurring in at least 5% of patients in the Dacogen group and at a rate greater than supportive care.

Table 4 Adverse Events Reported in ≥5% of Patients in the Dacogen Group and at a Rate Greater than Supportive Care in Phase 3 MDS Trial

	Dacogen N = 83 (%)	Supportive Care N = 81 (%)
Blood and lymphatic system disorders		
Neutropenia	75 (90)	58 (72)
Thrombocytopenia	74 (89)	64 (79)
Anemia NOS	68 (82)	60 (74)
Febrile neutropenia	24 (29)	5 (6)
Leukopenia NOS	23 (28)	11 (14)
Lymphadenopathy	10 (12)	6 (7)
Thrombocythemia	4 (5)	1 (1)
Cardiac disorders		
Pulmonary edema NOS	5 (6)	0 (0)
Eye disorders		
Vision blurred	5 (6)	0 (0)
Gastrointestinal disorders		
Nausea	35 (42)	13 (16)
Constipation	29 (35)	11 (14)
Diarrhea NOS	28 (34)	13 (16)
Vomiting NOS	21 (25)	7 (9)
Abdominal pain NOS	12 (14)	5 (6)
Oral mucosal petechiae	11 (13)	4 (5)
Stomatitis	10 (12)	5 (6)
Dyspepsia	10 (12)	1 (1)
Ascites	8 (10)	2 (2)
Gingival bleeding	7 (8)	5 (6)
Hemorrhoids	7 (8)	3 (4)
Loose stools	6 (7)	3 (4)
Tongue ulceration	6 (7)	2 (2)
Dysphagia	5 (6)	2 (2)
Oral soft tissue disorder NOS	5 (6)	1 (1)
Lip ulceration	4 (5)	3 (4)
Abdominal distension	4 (5)	1 (1)
Abdominal pain upper	4 (5)	1 (1)
Gastro-esophageal reflux disease	4 (5)	0 (0)
Glossodynia	4 (5)	0 (0)
General disorders and administrative site disorders		

	Dacogen N = 83 (%)	Supportive Care N = 81 (%)
Pyrexia	44 (53)	23 (28)
Edema peripheral	21 (25)	13 (16)
Rigors	18 (22)	14 (17)
Edema NOS	15 (18)	5 (6)
Pain NOS	11 (13)	5 (6)
Lethargy	10 (12)	3 (4)
Tenderness NOS	9 (11)	0 (0)
Fall	7 (8)	3 (4)
Chest discomfort	6 (7)	3 (4)
Intermittent pyrexia	5 (6)	3 (4)
Malaise	4 (5)	1 (1)
Crepitations NOS	4 (5)	1 (1)
Catheter site erythema	4 (5)	1 (1)
Catheter site pain	4 (5)	0 (0)
Injection site swelling	4 (5)	0 (0)
Hepatobiliary Disorders		
Hyperbilirubinemia	12 (14)	4 (5)
Infections and Infestations		
Pneumonia NOS	18 (22)	11 (14)
Cellulitis	10 (12)	6 (7)
Candidal infection NOS	8 (10)	1 (1)
Catheter related infection	7 (8)	0 (0)
Urinary tract infection NOS	6 (7)	1 (1)
Staphylococcal infection	6 (7)	0 (0)
Oral candidiasis	5 (6)	2 (2)
Sinusitis NOS	4 (5)	2 (2)
Bacteremia	4 (5)	0 (0)
Injury, poisoning and procedural complications		
Transfusion reaction	6 (7)	3 (4)
Abrasion NOS	4 (5)	1 (1)
Investigations		
Cardiac murmur NOS	13 (16)	9 (11)
Blood alkaline phosphatase NOS increased	9 (11)	7 (9)
Aspartate aminotransferase increased	8 (10)	7 (9)
Blood urea increased	8 (10)	1 (1)
Blood lactate dehydrogenase increased	7 (8)	5 (6)
Blood albumin decreased	6 (7)	0 (0)
Blood bicarbonate increased	5 (6)	1 (1)
Blood chloride decreased	5 (6)	1 (1)
Protein total decreased	4 (5)	3 (4)
Blood bicarbonate decreased	4 (5)	1 (1)
Blood bilirubin decreased	4 (5)	1 (1)
Metabolism and nutrition disorders		
Hyperglycemia NOS	27 (33)	16 (20)
Hypoalbuminemia	20 (24)	14 (17)

	Dacogen N = 83 (%)	Supportive Care N = 81 (%)
Hypomagnesemia	20 (24)	6 (7)
Hypokalemia	18 (22)	10 (12)
Hyponatremia	16 (19)	13 (16)
Appetite decreased NOS	13 (16)	12 (15)
Anorexia	13 (16)	8 (10)
Hyperkalemia	11 (13)	3 (4)
Dehydration	5 (6)	4 (5)
Musculoskeletal and connective tissue disorders		
Arthralgia	17 (20)	8 (10)
Pain in limb	16 (19)	8 (10)
Back pain	14 (17)	5 (6)
Chest wall pain	6 (7)	1 (1)
Musculoskeletal discomfort	5 (6)	0 (0)
Myalgia	4 (5)	1 (1)
Nervous system disorders		
Headache	23 (28)	11 (14)
Dizziness	15 (18)	10 (12)
Hypoesthesia	9 (11)	1 (1)
Psychiatric disorders		
Insomnia	23 (28)	11 (14)
Confusional state	10 (12)	3 (4)
Anxiety	9 (11)	8 (10)
Renal and urinary disorders		
Dysuria	5 (6)	3 (4)
Urinary frequency	4 (5)	1 (1)
Respiratory, thoracic and mediastinal disorders		
Cough	33 (40)	25 (31)
Pharyngitis	13 (16)	6 (7)
Crackles lung	12 (14)	1 (1)
Breath sounds decreased	8 (10)	7 (9)
Hypoxia	8 (10)	4 (5)
Rales	7 (8)	2 (2)
Postnasal drip	4 (5)	2 (2)
Skin and subcutaneous tissue disorders		
Ecchymosis	18 (22)	12 (15)
Rash NOS	16 (19)	7 (9)

	Dacogen N = 83 (%)	Supportive Care N = 81 (%)
Erythema	12 (14)	5 (6)
Skin lesion NOS	9 (11)	3 (4)
Pruritis	9 (11)	2 (2)
Alopecia	7 (8)	1 (1)
Urticaria NOS	5 (6)	1 (1)
Swelling face	5 (6)	0 (0)
Vascular disorders		
Petechiae	32 (39)	13 (16)
Pallor	19 (23)	10 (12)
Hypotension NOS	5 (6)	4 (5)
Hematoma NOS	4 (5)	3 (4)

Discussion of Clinically Important Adverse Reactions:

In the Phase 3 trial, the highest incidence of Grade 3 or Grade 4 adverse events in the Dacogen arm were neutropenia (87%), thrombocytopenia (85%), febrile neutropenia (23%) and leukopenia (22%). Bone marrow suppression was the most frequent cause of dose reduction, delay and discontinuation. Six patients had fatal events associated with their underlying disease and myelosuppression (anemia, neutropenia, and thrombocytopenia) that were considered at least possibly related to drug treatment. (See **PRECAUTIONS**). Of the 83 Dacogen-treated patients, 8 permanently discontinued therapy for adverse events; compared to 1 of 81 patients in the supportive care arm.

No overall difference in safety was detected between patients > 65 years of age and younger patients in these myelodysplasia trials. No significant gender differences in safety or efficacy were detected. Patients with renal or hepatic dysfunction were not studied. Insufficient numbers of non-white patients were available to draw conclusions in these clinical trials.

Serious Adverse Events that occurred in patients receiving Dacogen regardless of causality, not previously reported in **Table 4** include:

Blood and Lymphatic System Disorders: myelosuppression, splenomegaly.

Cardiac Disorders: myocardial infarction, congestive cardiac failure, cardio-respiratory arrest, cardiomyopathy, atrial fibrillation, supraventricular tachycardia.

Gastrointestinal Disorders: gingival pain, upper gastrointestinal hemorrhage.

General Disorders and Administrative Site Conditions: chest pain, asthenia, mucosal inflammation, catheter site hemorrhage.

Hepatobiliary Disorders: cholecystitis.

Infections and Infestations: fungal infection, sepsis, upper respiratory tract infection, bronchopulmonary aspergillosis, peridiverticular abscess, respiratory tract infection, pseudomonal lung infection, Mycobacterium avium complex infection.

Injury, poisoning and procedural complications: post procedural pain, post procedural hemorrhage.

Nervous system disorders: intracranial hemorrhage.

Psychiatric Disorders: mental status changes.

Renal and Urinary Disorders: renal failure, urethral hemorrhage.

Respiratory, Thoracic and Mediastinal Disorders: dyspnea, hemoptysis, lung infiltration, pulmonary embolism, respiratory arrest, pulmonary mass.

Allergic Reaction: Hypersensitivity (anaphylactic reaction) to Dacogen has been reported in a Phase 2 trial.

OVERDOSAGE

There is no known antidote for overdosage with Dacogen. Higher doses are associated with increased myelosuppression including prolonged neutropenia and thrombocytopenia. Standard supportive measures should be taken in the event of an overdose.

DOSAGE AND ADMINISTRATION

First Treatment Cycle

The recommended Dacogen dose is 15 mg/m^2 administered by continuous intravenous infusion over 3 hours repeated every 8 hours for 3 days. Patients may be premedicated with standard anti-emetic therapy.

Subsequent Treatment Cycles

The above cycle should be repeated every 6 weeks. It is recommended that patients be treated for a minimum of 4 cycles; however, a complete or partial response may take longer than 4 cycles. Treatment may be continued as long as the patient continues to benefit.

Dose Adjustment or Delay Based on Hematology Laboratory Values

If hematologic recovery (ANC ≥ 1,000/μL and platelets ≥ 50,000/μL) from a previous Dacogen treatment cycle requires more than 6 weeks, then the next cycle of Dacogen therapy should be delayed and dosing temporarily reduced by following this algorithm:

- Recovery requiring more than 6, but less than 8 weeks - Dacogen dosing to be delayed for up to 2 weeks and the dose temporarily reduced to 11 mg/m^2 every 8 hours (33 mg/m^2/day, 99 mg/m^2/cycle) upon restarting therapy.

- Recovery requiring more than 8, but less than 10 weeks - Patient should be assessed for disease progression (by bone marrow aspirates); in the absence of progression, the Dacogen dose should be delayed up to 2 more weeks and the dose reduced to 11 mg/m^2 every 8 hours (33 mg/m^2/day, 99 mg/m^2/cycle) upon restarting therapy, then maintained or increased in subsequent cycles as clinically indicated.

If any of the following non-hematologic toxicities are present, Dacogen treatment should not be restarted until the toxicity is resolved: 1) serum creatinine ≥ 2 mg/dL; 2) SGPT, total bilirubin ≥ 2 times ULN; and 3) active or uncontrolled infection.

Use in Geriatric Patients

Geriatric patients were generally dosed at the same level as younger adult patients. Dose adjustments for toxicity should be conducted as specified for the general population.

Preparation of Dacogen

Dacogen is a cytotoxic drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing Dacogen. Please refer to **Handling and Disposal** section.

Dacogen should be aseptically reconstituted with 10 mL of Sterile Water for Injection (USP); upon reconstitution, each mL contains approximately 5.0 mg of decitabine at pH 6.7-7.3. Immediately after reconstitution, the solution should be further diluted with 0.9% Sodium Chloride Injection, 5% Dextrose Injection, or Lactated Ringer's Injection to a final drug concentration of 0.1 - 1.0 mg/mL. Unless used within 15 minutes of reconstitution, the diluted solution must be prepared using cold (2˚C - 8˚C) infusion fluids and stored at 2˚C - 8˚C (36˚F 46˚F) for up to a maximum of 7 hours until administration.

HOW SUPPLIED

Dacogen™ (decitabine) for Injection is supplied as a sterile lyophilized white to almost white powder, in a single-dose vial, packaged in cartons of 1 vial. Each vial contains 50 mg of decitabine. **(NDC 58063-600-50).**

Storage

Store vials at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Stability

Unless used within 15 minutes of reconstitution, the diluted solution must be prepared using cold (2°C - 8°C) infusion fluids and stored at 2°C - 8°C (36°F - 46°F) for up to a maximum of 7 hours until administration.

Handling and Disposal

Procedures for proper handling and disposal of antineoplastic drugs should be applied. Several guidances on this subject have been published.[1-8] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

REFERENCES

1. ONS Clinical Practice Committee. Cancer Chemotherapy Guidelines and Recommendations for Practice Pittsburgh, Pa: Oncology Nursing Society; 1999:32-41.

2. National Institutes of Health. Recommendations for the safe handling of cytotoxic drugs. NIH Publication 92-2621. Available at: http://www.nih.gov/od/ors/ds/pubs/cyto/index.htm.

3. AMA Council on Scientific Affairs. Guidelines for handling parenteral neoplastics. *JAMA* 1985;253(11):1590-1592.

4. National Study Commission on Cytotoxic Exposure-Recommendations for handling cytotoxic agents. 1987. Available from Louis P. Jeffrey, Sc.D., Chairman, National Study Commission on Cytotoxic Exposure. Massachusetts College of Pharmacy and Allied Health Sciences, 179 Longwood Avenue, Boston, MA 02115.

5. Clinical Oncological Society of Australia. Guidelines and recommendations for safe handling of antineoplastic agents. *Med J Australia* 1983;1:426-428.

6. Jones RB, Frank R, Mass T. Safe handling of chemotherapeutic agents: A report from the Mount Sinai Medical Center. *CA-A Cancer J for Clin* 1983;33:258-263.

7. American Society of Hospital Pharmacists. ASHP Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs. *Am J Hosp Pharm* 1990;47:1033-1049.

8. Controlling Occupational Exposure to Hazardous Drugs. (OSHA Work-Practice Guidelines). *Am J Health-Syst Pharm* 1996;53:1669-1685.

MGI PHARMA, INC.

Manufactured by Pharmachemie B.V. Haarlem, The Netherlands

Manufactured for MGI PHARMA, INC., Bloomington, MN 55437

May 2006