

**CENTER FOR DRUG EVALUATION AND
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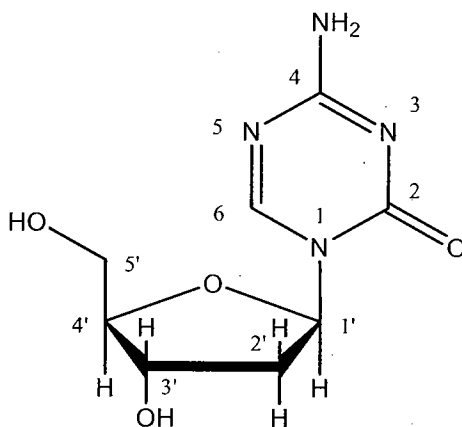
21-790

APPROVED LABELING

1 **DACOGEN™ (DECITABINE) FOR INJECTION**

2 **DESCRIPTION**

3 Dacogen™ (decitabine) for Injection contains decitabine (5-aza-2'-deoxycytidine), an analogue of the
4 natural nucleoside 2'-deoxycytidine. Decitabine is a fine, white to almost white powder with the
5 molecular formula of C₈H₁₂N₄O₄ and a molecular weight of 228.21. Its chemical name is 4-amino-1-(2-
6 deoxy-β-D-erythro-pentofuranosyl)-1,3,5-triazin-2(1H)-one and it has the following structural formula:



7
8 Decitabine is slightly soluble in ethanol/water (50/50), methanol/water (50/50) and methanol; sparingly
9 soluble in water and soluble in dimethylsulfoxide (DMSO).

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

13 **CLINICAL PHARMACOLOGY**

14 **Mechanism of Action**

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

23 **Pharmacokinetics**

24 No information is available on the pharmacokinetics of decitabine at the indicated dosage of 15 mg/m².
25 Patients with advanced solid tumors received a 72-hour infusion of decitabine at 20 to 30 mg/m²/day.

26 Decitabine pharmacokinetics were characterized by a biphasic disposition. The total body clearance
27 (mean ± SD) was 124 ± 19 L/hr/m², and the terminal phase elimination half-life was 0.51 ± 0.31 hr.
28 Plasma protein binding of decitabine is negligible (<1%).

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

32 **Special Populations**

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

35 **Drug-Drug Interactions**

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

41 **CLINICAL STUDIES**

42 **Phase 3 Trial**

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

52 **Table 1 Baseline Demographics and Other Patient Characteristics (ITT)**

Demographic or Other Patient Characteristic	Dacogen N=89	Supportive Care 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)

53

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

Demographic or Other Patient Characteristic	Dacogen N=89	Supportive Care N=81
FAB Classification n (%)		
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)

55

56 Patients randomized to the Dacogen arm received Dacogen intravenously infused at a dose of 15 mg/m²
 57 over a 3-hour period, every 8 hours, for 3 consecutive days. This cycle was repeated every 6 weeks,
 58 depending on the patient's clinical response and toxicity. Supportive care consisted of blood and blood
 59 product transfusions, prophylactic antibiotics, and hematopoietic growth factors. Co-primary endpoints
 60 of the study were overall response rate (complete response + partial response) and time to AML or
 61 death. Responses were classified using the MDS International Working Group (IWG) criteria; patients
 62 were required to be RBC and platelet transfusion independent during the time of response. Response
 63 criteria are given in **Table 2**:

64 **Table 2 Response Criteria for Phase 3 Trial***

Complete Response (CR) ≥ 8 weeks	Bone Marrow	On repeat aspirates: <ul style="list-style-type: none"> • < 5% myeloblasts • No dysplastic changes
	Peripheral Blood	In all samples during response: <ul style="list-style-type: none"> • 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 Response (PR) ≥ 8 weeks	Bone Marrow	On repeat aspirates: <ul style="list-style-type: none"> • ≥ 50% decrease in blasts over pretreatment values OR <ul style="list-style-type: none"> • Improvement to a less advanced MDS FAB classification
	Peripheral Blood	Same as for CR

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

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

77 **Table 3 Analysis of Response (ITT)**

Parameter	Dacogen N=89	Supportive Care 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.

78

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

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

82 **Phase 2 Studies**

83 Two additional open-label, single-arm, multicenter studies in Europe were conducted to evaluate the
 84 safety and efficacy of Dacogen in MDS patients with any of the FAB subtypes. Dacogen was
 85 intravenously infused at a dose of 15 mg/m² over a 4-hour period, every 8 hours, on days 1, 2 and 3 of
 86 week 1 every 6 weeks (1 cycle). The results of the Phase 2 studies were consistent with the results of
 87 the Phase 3 trial with overall response rates of 26% (N=66) and 24% (N=98).

88 **INDICATIONS AND USAGE**

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

94 **CONTRAINDICATIONS**

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

96 **WARNINGS**

97 **Pregnancy – Teratogenic effects: Pregnancy Category D**

98 Dacogen may cause fetal harm when administered to a pregnant woman. The developmental toxicity of
99 decitabine was examined in mice exposed to single IP (intraperitoneal) injections (0, 0.9 and 3.0 mg/m²,
100 approximately 2% and 7% of the recommended daily clinical dose, respectively) over gestation days 8,
101 9, 10 or 11. No maternal toxicity was observed but reduced fetal survival was observed after treatment
102 at 3 mg/m² and decreased fetal weight was observed at both dose levels. The 3 mg/m² dose elicited
103 characteristic fetal defects for each treatment day, including supernumerary ribs (both dose levels), fused
104 vertebrae and ribs, cleft palate, vertebral defects, hind-limb defects and digital defects of fore- and hind-
105 limbs. In rats given a single IP injection of 2.4, 3.6 or 6 mg/m² (approximately 5, 8 or 13% the daily
106 recommended clinical dose, respectively) on gestation days 9-12, no maternal toxicity was observed.
107 No live fetuses were seen at any dose when decitabine was injected on gestation day 9. A significant
108 decrease in fetal survival and reduced fetal weight at doses greater than 3.6 mg/m² was seen when
109 decitabine was given on gestation day 10. Increased incidences of vertebral and rib anomalies were seen
110 at all dose levels, and induction of exophthalmia, exencephaly, and cleft palate were observed at 6.0
111 mg/m². Increased incidence of foredigit defects was seen in fetuses at doses greater than 3.6 mg/m².
112 Reduced size and ossification of long bones of the fore-limb and hind-limb were noted at 6.0 mg/m².

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

117 **Use in Males**

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

121 **PRECAUTIONS**

122 **General**

123 Treatment with Dacogen is associated with neutropenia and thrombocytopenia. Complete blood and
124 platelet counts should be performed as needed to monitor response and toxicity, but at a minimum, prior
125 to each dosing cycle. After administration of the recommended dosage for the first cycle, dosage for
126 subsequent cycles should be adjusted as described in **DOSAGE AND ADMINISTRATION**. Clinicians
127 should consider the need for early institution of growth factors and/or antimicrobial agents for the
128 prevention or treatment of infections in patients with MDS. Myelosuppression and worsening
129 neutropenia may occur more frequently in the first or second treatment cycles, and may not necessarily
130 indicate progression of underlying MDS.

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

136 **Information for Patients**

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

138

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

141

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

144

145 **Laboratory Tests**

146

147 Complete blood counts and platelet counts should be performed as needed to monitor response and
148 toxicity, but at a minimum, prior to each cycle. Liver chemistries and serum creatinine should be
149 obtained prior to initiation of treatment.

150 **Drug-Drug Interactions**

151

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

154 **Carcinogenesis, Mutagenesis, and Impairment of Fertility**

155

156 No formal carcinogenicity evaluation of decitabine has been performed.

157

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

162 The effect of decitabine on postnatal development and reproductive capacity was evaluated in mice
163 administered a single 3 mg/m² IP injection (approximately 7% the recommended daily clinical dose) on
164 day 10 of gestation. Body weights of males and females exposed *in utero* to decitabine were
165 significantly reduced relative to controls at all postnatal time points. No consistent effect on fertility
166 was seen when female mice exposed *in utero* were mated to untreated males. Untreated females mated
167 to males exposed *in utero* showed decreased fertility at 3 and 5 months of age (36% and 0% pregnancy
168 rate, respectively). In male mice given IP injections of 0.15, 0.3 or 0.45 mg/m² decitabine
169 (approximately 0.3% to 1% the recommended clinical dose) 3 times a week for 7 weeks, decitabine did
170 not affect survival, body weight gain or hematological measures (hemoglobin and WBC counts). Testes
171 weights were reduced, abnormal histology was observed and significant decreases in sperm number
172 were found at doses ≥ 0.3 mg/m². In females mated to males dosed with ≥ 0.3 mg/m² decitabine,
173 pregnancy rate was reduced and preimplantation loss was significantly increased.

174

175 **Pregnancy**

176

177 **Teratogenic Effects: Category D. See WARNINGS section**

178

179 **Nursing Mothers:**

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

184

185 **Pediatric Use:**

186

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

188

189 **Geriatric Use:**

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

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

195

196 ADVERSE REACTIONS

197

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

200 Adverse Reactions Most Frequently ($\geq 1\%$) Resulting in Clinical Intervention in the Phase 3 Trial 201 in the Dacogen Arm:

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

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

207

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

210

211 Discussion of Adverse Reactions Information

212 Dacogen was studied in 2 single-arm Phase 2 studies (N = 66, N = 98) and 1 controlled Phase 3
213 (Supportive Care) study (N = 83 exposed to Dacogen). The data described below reflect exposure to
214 Dacogen in 83 patients in the Phase 3 MDS trial. In the Phase 3 trial, patients received 15 mg/m²
215 intravenously every 8 hours for 3 days every 6 weeks. The median number of Dacogen cycles was 3
216 (range 0 to 9).

217

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

220

221

222

223
 224

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)

225

226

227 **Discussion of Clinically Important Adverse Reactions:**

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

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

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

241 Blood and Lymphatic System Disorders: myelosuppression, splenomegaly.

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

244 Gastrointestinal Disorders: gingival pain, upper gastrointestinal hemorrhage.

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

247 Hepatobiliary Disorders: cholecystitis.

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

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

252 Nervous system disorders: intracranial hemorrhage.

253 Psychiatric Disorders: mental status changes.

254 Renal and Urinary Disorders: renal failure, urethral hemorrhage.

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

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

259

260

261 **OVERDOSAGE**

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

265 **DOSAGE AND ADMINISTRATION**

266 **First Treatment Cycle**

267 The recommended Dacogen dose is 15 mg/m² administered by continuous intravenous infusion over 3
268 hours repeated every 8 hours for 3 days. Patients may be premedicated with standard anti-emetic
269 therapy.

270 **Subsequent Treatment Cycles**

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

274 **Dose Adjustment or Delay Based on Hematology Laboratory Values**

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

- 278 • Recovery requiring more than 6, but less than 8 weeks - Dacogen dosing to be delayed for up to
279 2 weeks and the dose temporarily reduced to 11 mg/m² every 8 hours (33 mg/m²/day, 99
280 mg/m²/cycle) upon restarting therapy.

281 • Recovery requiring more than 8, but less than 10 weeks - Patient should be assessed for disease
282 progression (by bone marrow aspirates); in the absence of progression, the Dacogen dose should
283 be delayed up to 2 more weeks and the dose reduced to 11 mg/m² every 8 hours (33 mg/m²/day,
284 99 mg/m²/cycle) upon restarting therapy, then maintained or increased in subsequent cycles as
285 clinically indicated.

286

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

290 Use in Geriatric Patients

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

293 Preparation of Dacogen

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

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

302 HOW SUPPLIED

303 Dacogen™ (decitabine) for Injection is supplied as a sterile lyophilized white to almost white powder, in
304 a single-dose vial, packaged in cartons of 1 vial. Each vial contains 50 mg of decitabine. (NDC 58063-
305 600-50).

306 Storage

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

308 Stability

309

310 Unless used within 15 minutes of reconstitution, the diluted solution must be prepared using cold (2°C -
311 8°C) infusion fluids and stored at 2°C - 8°C (36°F - 46°F) for up to a maximum of 7 hours until
312 administration.

313 Handling and Disposal

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

317 REFERENCES

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319 Practice Pittsburgh, Pa: Oncology Nursing Society; 1999:32-41.
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- 332 7. American Society of Hospital Pharmacists. ASHP Technical Assistance Bulletin on Handling
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336 MGI PHARMA, INC.

337

338 Manufactured by Pharmachemie B.V. Haarlem, The Netherlands

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

340

May 2006

26x85 mm

93.175.105-A



1011003586060609

NDC 59663 600 50 By SRI
DACOGEN
 decitabine for injection
 50 mg per vial
 FOR INTRAVENOUS USE ONLY
 WARNING: Cytotoxic Agent
 Single use sterile vial
 Store vials at 25°C (77°F), excursions
 permitted to 15°-30° (59°-86°F)
 See insert

Each vial contains 50 mg
 decitabine, 60 mg miconazole
 potassium phosphate, and
 11.6 mg sodium hydroxide. See
 package insert and/or carton for
 detailed indications, contraindications,
 information, dosage information,
 and precautions.



MCI

Batch:

Exp.:

General information

Item number (version PCN) 93.175.105-A
 Name product Decitabine for injection, 50 mg/vial
 Lot no Supra-01210
 Used contents (quantity) 50x50
 Remarks

Authorization

MAC Centre signature:
 VV - 1 signature:
 VV - 2 signature:
 Label Owner signature: n.s.
 Quality Assurance signature:
 Purchase Opt signature:

Modifications

Change 01-00 03-02-05

Extra information

PCH 696
 afm. 44 x 44 x 90 mm
 size: 1,732 x 1,732 x 3,543 inch



50 mg per vial
 decitabine for injection
DACOGEN

NDC 58063-600-50

DACOGEN
 decitabine for injection
 50 mg per vial

FOR INTRAVENOUS USE ONLY

WARNING: Cytotoxic Agent
 Single use sterile vial

Rx ONLY

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

NDC 58063-600-50

See bottom flap for batch number
 and expiration date.

**KEEP THIS AND ALL MEDICATIONS
 OUT OF THE REACH OF CHILDREN.**

Manufactured by Pharmachemie B.V.
 Haarlem, The Netherlands

Manufactured for MGI PHARMA, INC.
 Bloomington, MN 55437



58063-600-50

NDC 58063-600-50

DACOGEN
 decitabine for injection
 50 mg per vial

FOR INTRAVENOUS USE ONLY

WARNING: Cytotoxic Agent
 Single use sterile vial

Rx ONLY

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

Each vial contains 50 mg decitabine, 68 mg
 monobasic potassium phosphate, and
 11.6 mg sodium hydroxide.

Reconstitution: Aseptically reconstitute
 with 10 mL of Sterile Water for Injection, USP;
 each mL will contain 5 mg of decitabine.

Final Concentration: The resultant solution
 will have a 5 mg per mL (5 mg/mL)
 concentration and pH of 6.7 to 7.3.

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.

See package insert for detailed indications,
 reconstitution information, dosage
 information, and precautions.



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 Bloomington, MN 55437 U.S.A.

batch no:

exp. date:

93.102.105-A
 050503
 PCH696
 1175/366

Art.nr: 51.212.255



Production Notes:
 456_021_TradePckg

Document size:
 Follow Die Line

Trim size:
 Follow Die Line

Color(s):
 5 color job
 C,M,Y,K
 Pantone 1935

Bleed(s):
 .0625" where needed

LIVE art:
 All art is LIVE
 unless noted.

The color called Non-Print
 Die Line does not print

General Information

Authorization

Item number + version PCH 93.102.105-A
 Name product Decitabine for injection, 50 mg per vial
 Lay out Superq n 1/01
 Used colours (+ pantol) PCH696, 050503
 Artending

MAC Centre
 VV - 1
 VV - 2
 Label Design
 Supply Assurance
 Purchase Dpt

signature:
 signature:
 signature:
 signature:
 signature:

Remarks

Modifications

Intra information

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Richard Pazdur
5/2/2006 02:45:58 PM