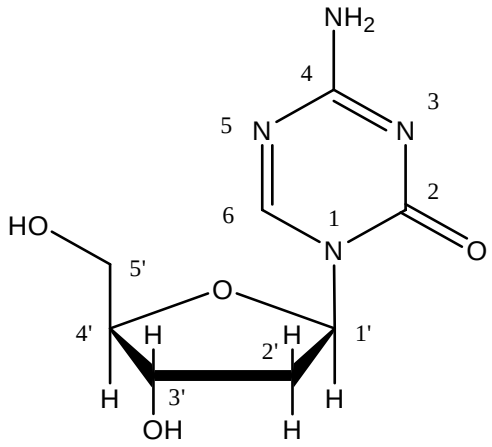
DACOGEN™ (DECITABINE) FOR INJECTION

DESCRIPTION

Dacogen™ (decitabine) for Injection contains decitabine (5-aza-2'-deoxycytidine), 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 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)

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)

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).

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