HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use DACOGEN safely and effectively. See full prescribing information for DACOGEN.

DACOGEN® (decitabine) for injection, for intravenous use
Initial U.S. Approval: 2006

---------- INDICATIONS AND USAGE ----------
DACOGEN is a nucleoside metabolic inhibitor indicated for treatment of adult 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. (1)

---------- DOSAGE AND ADMINISTRATION ----------
- Three Day Regimen: Administer DACOGEN at a dose of 15 mg/m^2 by continuous intravenous infusion over 3 hours repeated every 8 hours for 3 days. Repeat cycle every 6 weeks. (2.1)
- Five Day Regimen: Administer DACOGEN at a dose of 20 mg/m^2 by continuous intravenous infusion over 1 hour repeated daily for 5 days. Repeat cycle every 4 weeks. (2.1)

---------- DOSAGE FORMS AND STRENGTHS ----------
For Injection: 50 mg of decitabine as a lyophilized powder in a single-dose vial for reconstitution. (3)

---------- CONTRAINDICATIONS ----------
None.

---------- WARNINGS AND PRECAUTIONS ----------
- Neutropenia and Thrombocytopenia: Perform complete blood counts and platelet counts. (5.1)
- Embryo-Fetal Toxicity: Can cause fetal harm. Advise patients of reproductive potential of the potential risk to a fetus and to use effective contraception (5.2, 8.1, 8.3)

---------- ADVERSE REACTIONS ----------
Most common adverse reactions (> 50%) are neutropenia, thrombocytopenia, anemia, and pyrexia. (6.1)

---------- USE IN SPECIFIC POPULATIONS ----------
Lactation: Advise not to breastfeed. (8.2)

To report SUSPECTED ADVERSE REACTIONS, contact Otsuka America Pharmaceutical, Inc. at 1-800-438-9927 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 6/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage
2.2 Dosage Modifications for Adverse Reactions
2.3 Preparation and Administration
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Myelosuppression
5.2 Embryo-Fetal Toxicity
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility
14 CLINICAL STUDIES
14.1 Controlled Trial in Myelodysplastic Syndrome
14.2 Single-arm Studies in Myelodysplastic Syndrome
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

DACOGEN is indicated for treatment of adult 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.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

Pre-Medications and Baseline Testing

- Consider pre-medicating for nausea with antiemetics.
- Conduct baseline laboratory testing: complete blood count (CBC) with platelets, serum hepatic panel, and serum creatinine.

DACOGEN Regimen Options

Three Day Regimen

Administer DACOGEN at a dose of 15 mg/m^2 by continuous intravenous infusion over 3 hours repeated every 8 hours for 3 days. Repeat cycles every 6 weeks upon hematologic recovery (ANC at least 1,000/µL and platelets at least 50,000/µL) for a minimum of 4 cycles. A complete or partial response may take longer than 4 cycles. Delay and reduce dose for hematologic toxicity *[see Dosage and Administration (2.2)]*.

Five Day Regimen

Administer DACOGEN at a dose of 20 mg/m^2 by continuous intravenous infusion over 1 hour daily for 5 days. Delay and reduce dose for hematologic toxicity *[see Dosage and Administration (2.2)]*. Repeat cycles every 4 weeks upon hematologic recovery (ANC at least 1,000/µL and platelets at least 50,000/µL) for a minimum of 4 cycles. A complete or partial response may take longer than 4 cycles.

Patients with Renal or Severe Hepatic Impairment

Treatment with DACOGEN has not been studied in patients with pre-existing renal or hepatic impairment. For patients with pre-existing renal or hepatic impairment, consider the potential risks and benefits before initiating treatment with DACOGEN.

2.2 Dosage Modifications for Adverse Reactions

Hematologic Toxicity

If hematologic recovery from a previous DACOGEN treatment cycle requires more than 6 weeks, delay the next cycle of DACOGEN therapy and reduce DACOGEN dose temporarily by following this algorithm:

- Recovery requiring more than 6, but less than 8 weeks: delay DACOGEN dosing for up to 2 weeks and reduce the dose temporarily 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: Perform bone marrow aspirate to assess for disease progression. In the absence of progression, delay DACOGEN dosing for up to 2 more weeks and reduce the dose to 11 mg/m^2 every 8 hours (33 mg/m^2/day, 99 mg/m^2/cycle) upon restarting therapy, then maintain or increase dose in subsequent cycles as clinically indicated.

Non-hematologic Toxicity

Delay subsequent DACOGEN treatment for any the following nonhematologic toxicities and do not restart until toxicities resolve:

- Serum creatinine greater than or equal to 2 mg/dL
- Alanine transaminase (ALT), total bilirubin greater than or equal to 2 times upper limit of normal (ULN)
- Active or uncontrolled infection

2.3 Preparation and Administration

DACOGEN is a cytotoxic drug. Follow special handling and disposal procedures.[1]

Aseptically reconstitute DACOGEN with room temperature (20°C to 25°C) 10 mL of Sterile Water for Injection, USP. Upon reconstitution, the final concentration of the reconstituted DACOGEN solution is 5 mg/mL. You must dilute the reconstituted solution with 0.9% Sodium Chloride Injection or 5% Dextrose Injection prior to administration. Temperature of the diluent (0.9% Sodium Chloride Injection or 5% Dextrose Injection) depends on time of administration after preparation.

For Administration Within 15 Minutes of Preparation

If DACOGEN is intended to be administered within 15 minutes from the time of preparation, dilute the reconstituted solution with room temperature (20˚C to 25˚C) 0.9% Sodium Chloride Injection or 5% Dextrose Injection to a final concentration of 0.1 mg/mL to 1 mg/mL. Discard unused portion.

For Delayed Administration

If DACOGEN is intended to be administered after 15 minutes of preparation, dilute the reconstituted solution with cold (2˚C to 8˚C) 0.9% Sodium Chloride Injection or 5% Dextrose Injection to a final concentration of 0.1 mg/mL to 1 mg/mL. Store at 2˚C to 8˚C for up to 4 hours. Diluted stored solution must be used within 4 hours from the time of preparation. Discard unused portion.

Use the diluted, refrigerated solution within 4 hours from the time of preparation or discard.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if there is evidence of particulate matter or discoloration.

3 DOSAGE FORMS AND STRENGTHS

For Injection: 50 mg of decitabine as a sterile, white to almost white lyophilized powder in a single-dose vial for reconstitution

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Fatal and serious myelosuppression occurs in DACOGEN-treated patients. Myelosuppression (anemia, neutropenia, and thrombocytopenia) is the most frequent cause of DACOGEN dose reduction, delay, and discontinuation. Neutropenia of any grade occurred in 90% of DACOGEN-treated patients with grade 3 or 4 occurring in 87% of patients. Grade 3 or 4 febrile neutropenia occurred in 23% of patients. Thrombocytopenia of any grade occurred in 89% of patients with grade 3 or 4 occurring in 85% of patients. Anemia of any grade occurred in 82% of patients. Perform complete blood count with platelets

at baseline, prior to each cycle, and as needed to monitor response and toxicity. Manage toxicity using dose-delay, dose-reduction, growth factors, and anti-infective therapies as needed *[see Dosage and Administration (2.2)]*. Myelosuppression and worsening neutropenia may occur more frequently in the first or second treatment cycles and may not necessarily indicate progression of underlying MDS.

5.2 Embryo-Fetal Toxicity

Based on findings from human data, animal studies and its mechanism of action, DACOGEN can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1) and Nonclinical Toxicology (13.1)]*. In preclinical studies in mice and rats, decitabine caused adverse developmental outcomes including embryo-fetal lethality and malformations. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception while receiving DACOGEN and for 6 months following the last dose. Advise males with female partners of reproductive potential to use effective contraception while receiving treatment with DACOGEN and for 3 months following the last dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Myelosuppression *[see Warnings and Precautions (5.1)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of DACOGEN was studied in 3 single-arm studies (N = 66, N = 98, N = 99) and 1 controlled supportive care study (N = 83 DACOGEN, N = 81 supportive care). The data described below reflect exposure to DACOGEN in 83 patients in the MDS trial. In the 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).

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

Adverse Reactions Most Frequently (≥ 1%) Resulting in Clinical Intervention and or Dose Modification in the Controlled Supportive Care Study 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.

Table 1 presents all adverse reactions occurring in at least 5% of patients in the DACOGEN group and at a rate greater than supportive care.

Table 1 Adverse Reactions Reported in ≥ 5% of Patients in the DACOGEN Group and at a Rate Greater than Supportive Care in the Controlled Trial in MDS

	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		
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)

	DACOGEN N = 83 (%)	Supportive Care N = 81 (%)
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)
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)

	DACOGEN N = 83 (%)	Supportive Care N = 81 (%)
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)
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)

In a single-arm MDS study (N=99), DACOGEN was dosed at 20 mg/m^2 intravenously, infused over one hour daily, for 5 consecutive days of a 4-week cycle. Table 2 presents all adverse reactions occurring in at least 5% of patients.

Table 2 Adverse Reactions Reported in ≥ 5% of Patients in a Single-arm Study*

	DACOGEN N = 99 (%)
Blood and lymphatic system disorders	
Anemia	31 (31)
Febrile neutropenia	20 (20)
Leukopenia	6 (6)
Neutropenia	38 (38)
Pancytopenia	5 (5)
Thrombocythemia	5 (5)
Thrombocytopenia	27 (27)
Cardiac disorders	
Cardiac failure congestive	5 (5)
Tachycardia	8 (8)
Ear and labyrinth disorders	
Ear pain	6 (6)
Gastrointestinal disorders	
Abdominal pain	14 (14)
Abdominal pain upper	6 (6)
Constipation	30 (30)
Diarrhea	28 (28)
Dyspepsia	10 (10)
Dysphagia	5 (5)
Gastro-esophageal reflux disease	5 (5)
Nausea	40 (40)
Oral pain	5 (5)
Stomatitis	11 (11)
Toothache	6 (6)
Vomiting	16 (16)
General disorders and administration site conditions	
Asthenia	15 (15)
Chest pain	6 (6)
Chills	16 (16)
Fatigue	46 (46)
Mucosal inflammation	9 (9)
Edema	5 (5)
Edema peripheral	27 (27)
Pain	5 (5)
Pyrexia	36 (36)
Infections and infestations	
Cellulitis	9 (9)
Oral candidiasis	6 (6)
Pneumonia	20 (20)

	DACOGEN N = 99 (%)
Sinusitis	6 (6)
Staphylococcal bacteremia	8 (8)
Tooth abscess	5 (5)
Upper respiratory tract infection	10 (10)
Urinary tract infection	7 (7)
Injury, poisoning and procedural complications	
Contusion	9 (9)
Investigations	
Blood bilirubin increased	6 (6)
Breath sounds abnormal	5 (5)
Weight decreased	9 (9)
Metabolism and nutrition disorders	
Anorexia	23 (23)
Decreased appetite	8 (8)
Dehydration	8 (8)
Hyperglycemia	6 (6)
Hypokalemia	12 (12)
Hypomagnesemia	5 (5)
Musculoskeletal and connective tissue disorders	
Arthralgia	17 (17)
Back pain	18 (18)
Bone pain	6 (6)
Muscle spasms	7 (7)
Muscular weakness	5 (5)
Musculoskeletal pain	5 (5)
Myalgia	9 (9)
Pain in extremity	18 (18)
Nervous system disorders	
Dizziness	21 (21)
Headache	23 (23)
Psychiatric disorders	
Anxiety	9 (9)
Confusional state	8 (8)
Depression	9 (9)
Insomnia	14 (14)
Respiratory, thoracic and mediastinal disorders	
Cough	27 (27)
Dyspnea	29 (29)
Epistaxis	13 (13)
Pharyngolaryngeal pain	8 (8)
Pleural effusion	5 (5)
Sinus congestion	5 (5)
Skin and subcutaneous tissue disorders	
Dry skin	8 (8)
Ecchymosis	9 (9)

	DACOGEN N = 99 (%)
Erythema	5 (5)
Night sweats	5 (5)
Petechiae	12 (12)
Pruritus	9 (9)
Rash	11 (11)
Skin lesion	5 (5)
Vascular disorders	
Hypertension	6 (6)
Hypotension	11 (11)

* In this single arm study, investigators reported adverse events based on clinical signs and symptoms rather than predefined laboratory abnormalities. Thus, not all laboratory abnormalities were recorded as adverse events.

No overall difference in safety was detected between patients > 65 years of age and younger patients in these MDS trials. No significant differences in safety were detected between males and females. 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 reactions that occurred in patients receiving DACOGEN not previously reported in Tables 1 and 2 include:

- Allergic Reaction: hypersensitivity (anaphylactic reaction)
- Blood and Lymphatic System Disorders: myelosuppression, splenomegaly
- Cardiac Disorders: myocardial infarction, cardio-respiratory arrest, cardiomyopathy, atrial fibrillation, supraventricular tachycardia
- Gastrointestinal Disorders: gingival pain, upper gastrointestinal hemorrhage
- General Disorders and Administrative Site Conditions: chest pain, catheter site hemorrhage
- Hepatobiliary Disorders: cholecystitis
- Infections and Infestations: fungal infection, sepsis, 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: hemoptysis, lung infiltration, pulmonary embolism, respiratory arrest, pulmonary mass

6.2 Postmarketing Experience

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

- Sweet's syndrome (acute febrile neutrophilic dermatosis)
- Differentiation syndrome
- Interstitial lung disease

7 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 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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings from human data, animal studies, and the mechanism of action, DACOGEN can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1) and Nonclinical Toxicology (13.1)]*. Limited published data on DACOGEN use throughout the first trimester during pregnancy describe adverse developmental outcomes including major birth defects (structural abnormalities). In animal reproduction studies, administration of decitabine to pregnant mice and rats during organogenesis caused adverse developmental outcomes including malformations and embryo-fetal lethality starting at doses approximately 7% of the recommended human dose on a mg/m^2 basis *(see Data)*. Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The estimated background risk of major birth defects and miscarriage in the U.S. general population is 2% to 4% and 15% to 20% of clinically recognized pregnancies, respectively.

Data

Human Data

A single published case report of decitabine pregnancy exposure in a 39-year old woman with a hematologic malignancy described multiple structural abnormalities after 6 cycles of therapy in the 18th week of gestation. These abnormalities included holoprosencephaly, absence of nasal bone, mid-facial deformity, cleft lip and palate, polydactyly and rocker-bottom feet. The pregnancy was terminated.

Animal Data

In utero exposure to decitabine causes temporal related defects in the rat and/or mouse, which include growth suppression, exencephaly, defective skull bones, rib/sternabrae defects, phocomelia, digit defects, micrognathia, gastroschisis, micromelia. Decitabine inhibits proliferation and increases apoptosis of neural progenitor cells of the fetal CNS and induces palatal clefting in the developing murine fetus. Studies in mice have also shown that decitabine administration during osteoblastogenesis (day 10 of gestation) induces bone loss in offspring.

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.

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). Follow up studies indicated that treatment of pregnant mice with decitabine on gestation day 10 was associated with a reduced pregnancy rate resulting from effects on sperm production in the F1-generation.

8.2 Lactation

Risk Summary

There are no data on the presence of decitabine or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions from DACOGEN in a breastfed child, advise women not to breastfeed while receiving DACOGEN and for at least 2 weeks after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Conduct pregnancy testing of females of reproductive potential prior to initiating DACOGEN.

Contraception

Females

DACOGEN can cause fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception while receiving DACOGEN and for 6 months following the last dose.

Males

Advise males with female partners of reproductive potential to use effective contraception while receiving treatment with DACOGEN and for 3 months following the last dose *[see Nonclinical Toxicology (13.1)]*.

Infertility

Based on findings of decitabine in animals, male fertility may be compromised by treatment with DACOGEN. The reversibility of the effect on fertility is unknown *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

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

8.5 Geriatric Use

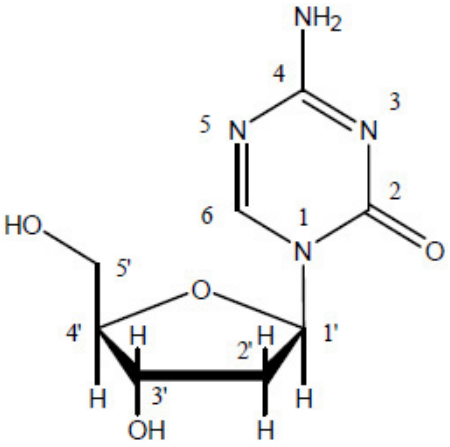
Of the total number of patients exposed to DACOGEN in the controlled clinical trial, 61 of 83 patients were age 65 years and over, while 21 of 83 patients were age 75 years and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other 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.

10 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.

11 DESCRIPTION

Decitabine is a nucleoside metabolic inhibitor. 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, for intravenous use, is a sterile, white to almost white lyophilized powder supplied in a clear colorless glass single-dose vial. Each 20 mL vial contains 50 mg decitabine, 68 mg monobasic potassium phosphate (potassium dihydrogen phosphate) and 11.6 mg sodium hydroxide. Sodium hydroxide and/or hydrochloric acid are used for pH adjustment.

12 CLINICAL PHARMACOLOGY

12.1 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.

12.2 Pharmacodynamics

Decitabine has been shown to induce hypomethylation both in vitro and in vivo. However, there have been no studies of decitabine-induced hypomethylation and pharmacokinetic parameters.

12.3 Pharmacokinetics

Pharmacokinetic (PK) parameters were evaluated in patients. Eleven patients received 20 mg/m^2 infused over 1 hour intravenously (treatment Option 2). Fourteen patients received 15 mg/m^2 infused over 3 hours

intravenously (treatment Option 1). PK parameters are shown in Table 3. Plasma concentration-time profiles after discontinuation of infusion showed a biexponential decline. The clearance (CL) of decitabine was higher following treatment Option 2. Upon repeat doses, there was no systemic accumulation of decitabine or any changes in PK parameters. Population PK analysis (N=35) showed that the cumulative AUC per cycle for treatment Option 2 was 2.3-fold lower than the cumulative AUC per cycle following treatment Option 1.

Table 3 Mean (CV% or 95% CI) Pharmacokinetic Parameters of Decitabine

Dose	C_{max} (ng/mL)	$AUC_{0\text{-}INF}$ (ng·h/mL)	$T_{1/2}$ (h)	CL (L/h/m^2)	$AUC_{Cumulative}$‡ (ng·h/mL)
15 mg/m^2 3-hr infusion every 8 hours for 3 days (Option 1)*	73.8 (66)	163 (62)	0.62 (49)	125 (53)	1332 (1010-1730)
20 mg/m^2 1-hr infusion daily for 5 days (Option 2)†	147 (49)	115 (43)	0.54 (43)	210 (47)	570 (470-700)

*N=14, †N=11, ‡N=35 Cumulative AUC per cycle

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.

Specific Populations

Patients with Renal Impairment

There are no data on the use of DACOGEN in patients with renal impairment.

Patients with Hepatic Impairment

There are no data on the use of DACOGEN in patients with hepatic impairment.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility

Carcinogenicity studies with decitabine have not been conducted.

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.

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 white blood cell 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.

14 CLINICAL STUDIES

14.1 Controlled Trial in Myelodysplastic Syndrome

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 4.

Table 4 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)
Sex 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)
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. The study endpoints 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 5.

Table 5 Response Criteria for the Controlled Trial in MDS*

Complete Response (CR) ≥ 8 weeks	**Bone Marrow**	**On repeat aspirates:** • < 5% myeloblasts • No dysplastic changes
	Peripheral Blood	**In all samples during response:** • Hgb > 11 g/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:** • ≥ 50% decrease in blasts over pretreatment values OR • Improvement to a less advanced MDS FAB classification
	Peripheral Blood	**Same as for CR**

*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 6). 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 6 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 statistical analysis plan, 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.

14.2 Single-arm Studies in Myelodysplastic Syndrome

Three open-label, single-arm, multicenter studies were conducted to evaluate the safety and efficacy of DACOGEN in MDS patients with any of the FAB subtypes. In one study conducted in North America, 99 patients with IPSS Intermediate-1, Intermediate-2, or high-risk prognostic scores received DACOGEN

20 mg/m^2 as an intravenous infusion over 1-hour daily, on days 1-5 of week 1, every 4 weeks (1 cycle). The results were consistent with the results of the controlled trial and are summarized in Table 8.

Table 7 Baseline Demographics and Other Patient Characteristics (ITT)

Demographic or Other Patient Characteristic	DACOGEN N = 99
Age (years)	
Mean (±SD)	71±9
Median (Range: min-max)	72 (34-87)
Sex n (%)	
Male	71 (72)
Female	28 (28)
Race n (%)	
White	86 (87)
Black	6 (6)
Asian	4 (4)
Other	3 (3)
Days From MDS Diagnosis to First Dose	
Mean (±SD)	444±626
Median (Range: min-max)	154 (7-3079)
Previous MDS Therapy n (%)	
Yes	27 (27)
No	72 (73)
RBC Transfusion Status n (%)	
Independent	33 (33)
Dependent	66 (67)
Platelet Transfusion Status n (%)	
Independent	84 (85)
Dependent	15 (15)
IPSS Classification n (%)	
Low Risk	1 (1)
Intermediate–1	52 (53)
Intermediate–2	23 (23)
High Risk	23 (23)
FAB Classification n (%)	
RA	20 (20)
RARS	17 (17)
RAEB	45 (45)
RAEB-t	6 (6)
CMML	11 (11)

Table 8 Analysis of Response (ITT)*

Parameter	DACOGEN N=99
Overall Response Rate (CR+PR)	**16 (16%)**
Complete Response (CR)	15 (15%)
Partial Response (PR)	1 (1%)

Duration of Response	
Median time to (CR+PR) response - Days (range)	162 (50-267)
Median Duration of (CR+PR) response - Days (range)	443 (72-722[†])

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

15 REFERENCES

1. OSHA Hazardous Drugs." OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html

16 HOW SUPPLIED/STORAGE AND HANDLING

DACOGEN for injection is a sterile, white to almost white lyophilized powder for intravenous use supplied as:

NDC 59148-046-70, 50 mg single-dose vial individually packaged in a carton.

Store vials at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [See USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Myelosuppression

Advise patients of the risk of myelosuppression and to report any symptoms of infection, anemia, or bleeding to their healthcare provider as soon as possible. Advise patients for the need for laboratory monitoring *[see Warnings and Precautions (5.1)]*.

Embryo-Fetal Toxicity

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy *[see Warnings and Precautions (5.2) and Use in Specific Populations (8.1)]*.

Advise females of reproductive potential to use effective contraception while receiving DACOGEN and for 6 months after last dose *[see Use in Specific Populations (8.3)]*.

Advise males with female partners of reproductive potential to use effective contraception while receiving treatment with DACOGEN and for 3 months after the last dose *[see Use in Specific Populations (8.3)* and *Nonclinical Toxicology (13.1)]*.

Lactation

Advise women to avoid breastfeeding while receiving DACOGEN and for at least 2 weeks after the last dose *[see Use in Specific Populations (8.2)]*.

Otsuka America Pharmaceutical, Inc.
Manufactured by Pharmachemie B.V. Haarlem, The Netherlands
Manufactured for Otsuka America Pharmaceutical, Inc., Rockville, MD 20850 USA

DACOGEN is a registered trademark of Astex Pharmaceuticals, Inc.,
Dublin, CA, U.S.A. used under license.