PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrDACOGEN®

Decitabine for Injection

Powder 50 mg/vial, Intravenous

Antineoplastic Agent – Pyrimidine Analogue

Otsuka Pharmaceutical Co., Ltd.
Tokyo, 101-8535 Japan

Date of Preparation:
December 17, 2019

Imported and Distributed by:
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Oakville, Ontario
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Submission Control No: 217663

RECENT MAJOR LABEL CHANGES

Not applicable

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

DACOGEN® (decitabine) is indicated for the treatment of adult patients with *de novo* or secondary Myelodysplastic Syndrome (MDS), untreated or previously treated with chemotherapy, who are not considered candidates for hematopoietic stem cell transplantation, including:

- Intermediate-1, intermediate-2 and high-risk International Prognostic Scoring System (IPSS) groups,
- All French-American-British (FAB) subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia (CMML)).

1.1 Pediatrics

Pediatrics (< 18 years of age): MDS is rare in children. DACOGEN is not indicated in the pediatric population, as the safety and efficacy of DACOGEN has not been studied in patients less than 18 years of age.

1.2 Geriatrics

Geriatrics (> 65 years of age): No overall differences in safety or effectiveness were observed between patients 65 years and older as compared to younger subjects. However, in older individuals (75 years and older) catheter related infections (5% in patients 65 and older vs. 24% in patients 75 years and older) were reported more frequently in a phase 3 clinical trial.

2 CONTRAINDICATIONS

DACOGEN is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 SERIOUS WARNINGS AND PRECAUTIONS BOX

DACOGEN should only be administered by healthcare professionals experienced in the use of antineoplastic agents.

- Neutropenia and Thrombocytopenia (see WARNINGS AND PRECAUTIONS, Hematologic).
- Potential for fetal harm (see WARNINGS AND PRECAUTIONS, Sexual Health, Reproduction, Special Populations, Pregnant Women).

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

DACOGEN must be administered under the supervision of a qualified physician experienced in the use of chemotherapeutic agents.

Patients may be premedicated with standard anti-emetic therapy. A mild to moderate increase in nausea, vomiting and diarrhea was reported in patients receiving DACOGEN. (See ADVERSE REACTIONS).

Two dosing regimens are recommended. With either regimen 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. 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.

Treatment may be delayed at the discretion of the treating physician, if patients experience hematological or non-hematological adverse reactions (see Recommended Dose and Dosage Adjustment).

If after 4 cycles, the patient's hematological values (e.g., platelet counts or absolute neutrophil count), have not returned to pre-treatment levels or if disease progression occurs (peripheral blast counts are increasing or bone marrow blast counts are worsening), the patient may be considered to be a non-responder and alternative therapeutic options to DACOGEN should be considered.

Dosage should be modified in the presence of hematological and non-hematological toxicities.

4.2 Recommended Dose and Dosage Adjustment

Recommended Dose

There are two possible treatment regimens for DACOGEN.

Option 1: In Patient (3-Day Dosing Regimen)

DACOGEN is administered at a dose of 15 mg/m^2 body surface area by continuous intravenous infusion over 3 hours repeated every 8 hours for 3 consecutive days. This cycle should be repeated every 6 weeks depending on the patient's clinical response and observed toxicity.

Option 2: Out Patient (5-Day Dosing Regimen)

DACOGEN is administered at a dose of 20 mg/m^2 body surface area by continuous intravenous infusion over 1 hour repeated daily for 5 consecutive days. This cycle should be repeated every 4 weeks depending on the patient's clinical response and observed toxicity.

Dosage Adjustment

If patients experience toxicities as described below DACOGEN dosage should be adjusted.

Non-Hematologic Toxicity
DACOGEN treatment should be delayed subsequent to any the following non-hematologic toxicities and should not be restarted until toxicities resolve:

- Serum creatinine ≥ 2 mg/dL
- SGPT, total bilirubin ≥ 2 times ULN
- Active or uncontrolled infection

Hematologic Toxicity
Myelosuppression and adverse events related to myelosuppression (thrombocytopenia, anemia, neutropenia, and febrile neutropenia) are common in both treated and untreated patients. Complications of myelosuppression include infections and bleeding. Treatment may be delayed at the discretion of the treating physician, if the patient experiences myelosuppression-associated complications, such as those described below. Treatment with DACOGEN may be resumed once these conditions have improved or have been stabilized with adequate treatment (anti-infective therapy, transfusion, or growth factors).

- Febrile neutropenia (temperature ≥ 38.5°C and absolute neutrophil count (ANC) < 1,000/µL)
- Active viral, bacterial or fungal infection (i.e., requiring intravenous anti-infectives or extensive supportive care)
- Hemorrhage (gastrointestinal, genito-urinary, pulmonary with platelets < 25,000/µL or any central nervous system hemorrhage). (See WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS).

Option 1: In Patient (3-Day Dosing Regimen)

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

- If DACOGEN treatment is required for more than 6, but less than 8 weeks –DACOGEN dosing should be delayed for up to 2 weeks and the dose should be temporarily reduced to 11 mg/m^2 by surface area every 8 hours (33 mg/m^2/day, 99 mg/m^2/cycle) upon restarting therapy.
- If DACOGEN treatment is required for more than 8, but less than 10 weeks - bone marrow aspirate should be performed to assess for disease progression. In the absence of progression, DACOGEN dose should be delayed up to 2 more weeks and the dose should be reduced to 11 mg/m^2 by surface area every 8 hours (33 mg/m^2/day, 99 mg/m^2/cycle) upon restarting therapy, then the dose should be maintained or increased in subsequent cycles as clinically indicated.

Option 2: Out Patient (5-Day Dosing Regimen)

Dose reduction is not recommended for the 5-day dosing regimen.

If hematologic recovery (ANC at least 1,000/µL and platelets at least 50,000/µL) from a previous DACOGEN treatment cycle requires more than 4 weeks, DACOGEN therapy should be delayed to the next cycle.

Pediatrics (< 18 years of age): There is no safety and efficacy data available from children. MDS occurs rarely in children.

Geriatrics (> 65 years of age): No overall differences in safety or effectiveness were observed between patient 65 years and older as compared to younger subjects. However, in older individuals (75 years and older) catheter related infections (5% in patients 65 and older vs. 24% in patients 75 years and older) were reported more frequently in a phase 3 clinical trial.

Renal Impairment: Patients with renal impairment were excluded from the trials. Decitabine is mainly excreted (90%) in the urine. DACOGEN should be used with caution in renal impairment and these patients should be monitored closely for toxicity including worsening of renal function. Serum creatinine should be obtained prior to initiation of treatment if non-hematologic toxicities are present. DACOGEN treatment should not be restarted until serum creatinine ≥ 2 mg/dL. (See ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Hepatic Impairment: There are no data on patients with hepatic impairment because they were excluded from the trials. Hyperbilirubinemia appeared as an early event. DACOGEN should be used with caution and liver function tests should be monitored closely during DACOGEN treatment. Liver chemistries should be obtained prior to initiation of treatment and if non-hematologic toxicities are present. DACOGEN treatment should not be restarted until ALT and total bilirubin ≥ 2x ULN. (See ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

4.3 Administration

DACOGEN is administered by intravenous infusion.

DACOGEN is a cytotoxic drug and caution should be exercised when handling and preparing DACOGEN. Procedures for proper handling and disposal of antineoplastic drugs should be applied (see SPECIAL HANDLING INSTRUCTIONS).

4.4 Reconstitution

DACOGEN should be aseptically reconstituted with 10 mL of Sterile Water for Injection (SWI) at room temperature; gently swirl to dissolve and ensure the solution is clear (no visible undissolved matter. Upon reconstitution, each mL contains approximately 5 mg of decitabine at pH 6.7-7.3.

Table 1 – Reconstitution

Vial Size	Volume of Diluent to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
50 mg lyophilized powder	10 mL	10 mL	5 mg/mL

If administration is planned within 15 minutes of reconstitution, the reconstituted solution should immediately be further diluted as per the recommended procedure with infusion fluids, such as 0.9% Sodium Chloride Injection or 5% Dextrose Injection to a final drug concentration of 0.1 – 1 mg/mL.

Unless administration of the diluted solution is started within 15 minutes of reconstitution, the reconstituted solution must be further diluted with **cold** (2-8°C) infusion fluids and stored at 2-8°C for a maximum of 4 hours until administration (see STORAGE, STABILITY AND DISPOSAL).

Inspect the diluted product visually for particulate matter and discoloration prior to administration. DO NOT use if solution appears hazy, contains particles.

Check the container for minute leaks prior to use by squeezing the bag firmly; ensure that the seal is intact. If leaks are found, discard the solution as sterility may be impaired.

4.5 Missed Dose

If a dose is missed, treatment should be resumed as soon as possible.

5 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 initiated in the event of an overdose.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 2 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous infusion	Single-use clear colorless glass vials containing 50 mg lyophilized powder for solution for infusion, with a potency of 5 mg/mL upon reconstitution.	Potassium dihydrogen phosphate, sodium hydroxide

7 WARNINGS AND PRECAUTIONS

General

DACOGEN administration should only be administered by healthcare professionals experienced with cancer chemotherapeutic drugs.
DACOGEN is a cytotoxic drug and caution should be exercised while handling and disposal of DACOGEN. See DOSAGE AND ADMINISTRATION; SPECIAL HANDLING INSTRUCTIONS.

There is a risk of DACOGEN degradation at room temperature if not used within 15 minutes of reconstitution. Therefore, DACOGEN should be diluted with cold recommended infusion fluids and stored at 2-8°C for a maximum of 4 hours until administration (see DOSAGE AND ADMINISTRATION, Administration, Reconstitution, STORAGE, STABILITY AND DISPOSAL).

Carcinogenesis and Mutagenesis
Carcinogenicity studies with decitabine have not been conducted. Decitabine is mutagenic in vitro and in vivo studies. (See NON-CLINICAL TOXICOLOGY).

Cardiovascular
No thorough clinical QT/QTc study have been conducted. Patients with a history of severe congestive heart failure or clinically unstable cardiac disease were excluded from clinical studies and therefore the safety and efficacy of DACOGEN in these patients has not been established. Patients with history of severe congestive heart failure or clinically unstable cardiac disease should be closely monitored. (See NON-CLINICAL TOXICOLOGY).

Driving and Operating Machinery
Patients should be advised that they may experience fatigue, dizziness, confusional state, and blurred vision due to anemia during treatment. Due caution should be exercised when driving or operating a vehicle or potentially dangerous machinery.

Hematologic
Hemorrhage
Serious bleeding-related adverse reactions (AR) such as central nervous system (CNS) haemorrhage (1%) and gastrointestinal (GI) haemorrhage (2%), were reported due to severe thrombocytopenia in patients receiving DACOGEN. Patients receiving DACOGEN should be monitored closely for signs and symptoms of serious bleeding-related adverse events. (See ADVERSE REACTIONS).

Myelosuppression
Complete blood and platelet counts should be performed regularly, as clinically indicated and prior to each treatment cycle. In the presence of myelosuppression or its complications, DACOGEN may be interrupted or supportive measures such as growth factor support (e.g. G-CSF) for neutropenia and red blood cell or platelet transfusions or antimicrobial agents for the prevention and treatment of myelosuppression or infections may be instituted according to institutional guidelines. (See WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests, DOSAGE AND ADMINISTRATION).

Increased risk of febrile neutropenia, worsening of neutropenia from Grade 3 to Grade 4 (in 85% patients) and increased requirements for transfusion occurred in the first two treatment cycles. Myelosuppression and complications of myelosuppression, including infections and bleeding that occur in patients with MDS may be exacerbated with DACOGEN treatment. The highest incidence of Grade 3 and/or Grade 4 ARs with neutropenia (87%), thrombocytopenia (85%), febrile neutropenia (23%) and leukopenia (22%) occurred with DACOGEN. Additionally, eight patients had fatal events due to infection and/or bleeding that were considered at least possibly related to DACOGEN treatment. Fungal infections and bacteremia appeared as early events, as do febrile neutropenia, rigor and hyperbilirubinemia. (See ADVERSE REACTIONS).

Hepatic
There are no data in patients with hepatic impairment because these patients were excluded from the trials. Hyperbilirubinemia appeared as an early event. DACOGEN should be used with caution and liver function tests should be monitored closely during DACOGEN treatment (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Immune

Hypersensitivity

Hypersensitivity reactions including serious anaphylactic reactions have been reported with DACOGEN. Skin and subcutaneous events and petechiae also appeared early, but diminish more slowly than other early events. DACOGEN treatment should be discontinued for serious adverse reactions. Supportive treatment should be initiated promptly. (See ADVERSE REACTIONS).

Infections and Infestations:

Serious infection-related adverse reactions such as septic shock, sepsis, and pneumonia were reported in patients receiving DACOGEN. Infections were reported with higher frequency early in treatment during Cycles 1 and 2. Fungal infections and bacteremia appeared as early events, as did febrile neutropenia. Patients should be monitored for signs and symptoms of infection and supportive prophylactic antibiotics and treatment should be initiated promptly. (See ADVERSE REACTIONS).

Monitoring and Laboratory Tests

Complete blood and platelet counts should be performed to monitor response and toxicity as needed, but at a minimum prior to each dose. Liver chemistries and serum creatinine should be obtained prior to initiation of treatment and if signs and symptoms of liver/renal toxicities are suspected. (See Hematologic, ADVERSE REACTIONS).

Renal

Patients with renal impairment were excluded from the trials. Decitabine is mainly excreted (90%) in the urine. DACOGEN should be used with caution and these patients should be monitored closely. (See ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics).

Respiratory thoracic and mediastinal disorders

Cases of interstitial lung disease (ILD) (including pulmonary infiltrates, organising pneumonia and pulmonary fibrosis) without signs of infectious aetiology have been reported in patients receiving decitabine. Careful assessment of patients with an acute onset or unexplained worsening of pulmonary symptoms should be performed to exclude ILD. If ILD is confirmed, appropriate treatment should be initiated. (See ADVERSE REACTIONS).

Sexual Health

Reproduction

Women of childbearing potential should be advised to avoid becoming pregnant and should be counseled to use effective contraception while receiving DACOGEN. Based on its mechanism of action, DACOGEN alters DNA synthesis and can cause fetal harm. The time period following treatment with DACOGEN where it is safe to become pregnant is unknown.

Men should be advised not to father a child while receiving treatment with DACOGEN, and for 3 months following completion of treatment. Men with female partners of childbearing potential should use effective contraception during this time. (See ACTION AND CLINICAL PHARMACOLOGY, Mechanism of Action; NON-CLINICAL TOXICOLOGY).

Fertility

In vivo studies demonstrated significant decreases in sperm counts in mice administered half of the decitabine recommended dose in humans. Because of the possibility of infertility as a consequence of DACOGEN therapy, men should be advised to seek advice on conservation of sperm prior to any DACOGEN treatment and female patients of childbearing potential should seek consultation regarding oocyte cryopreservation prior to initiation of treatment. (See NON-CLINICAL TOXICOLOGY).

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate data and well-controlled studies of DACOGEN in pregnant women.

Decitabine is teratogenic in embryo-fetal studies in rats and mice, in the absence of maternal toxicity. Based on results from animal studies and its mechanism of action, DACOGEN can cause fetal harm and therefore should not be used during pregnancy. If DACOGEN is to be used in pregnant woman, or if the patient becomes pregnant while taking DACOGEN, the patient should be apprised of the potential hazard to the fetus. (See NON-CLINICAL TOXICOLOGY).

7.1.2 Breast-feeding

It is not known whether decitabine or its metabolites are excreted in breast milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants who are exposed to decitabine, mothers should be advised not to breast-feed while undergoing therapy with DACOGEN.

7.1.3 Pediatrics

Pediatrics (< 18 years): There is no safety and efficacy data available from children. MDS occurs rarely in children. Lack of efficacy was reported from clinical studies in children with Acute Myeloid Leukemia (AML) receiving DACOGEN in sequential/combination with other drugs. It is unlikely that DACOGEN priming prior to induction therapy will improve the remission rate of pediatric subjects with AML.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): No overall differences in safety or effectiveness were observed between patients 65 years and older as compared to younger subjects. However, in older individuals (75 years and older) catheter related infections (5% in patients 65 and older vs. 24% in patients 75 years and older) were reported more frequently in a phase 3 clinical trial. (See CLINICAL TRIALS).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The safety of DACOGEN in MDS adult patients was studied in a single-arm study (N = 99) and a controlled supportive care trial (N = 83 DACOGEN, N = 81 supportive care). In the controlled supportive care trial, patients received 15 mg/m^2 DACOGEN by body surface area intravenously every 8 hours for 3 days every 6 weeks. In the single-arm MDS study (N=99) DACOGEN was dosed at 20 mg/m^2 intravenously infused by body surface area, over one hour daily for 5 consecutive days of a 4-week cycle. Patients with a history of uncontrolled cardiac disease or congestive heart failure, renal dysfunction or, hepatic dysfunction were excluded.

The safety profile of DACOGEN using the 3-day and 5-day regimens are similar in that the most common adverse reactions were blood and lymphatic systems disorders: mainly myelosuppression (neutropenia, thrombocytopenia, anemia, and febrile neutropenia). The incidence of these adverse reactions were lower in patients treated with the 5-day regimen. In the first two treatment cycles, there was an increased risk of febrile neutropenia and increased requirements for transfusion which were not seen in later cycles. Dose-related, but transient cytopenias, were reported early in the treatment regimen following the initial DACOGEN infusions. Serious infection-related adverse reactions such as septic shock, sepsis, and pneumonia were reported in patients receiving DACOGEN.

Serious bleeding-related adverse reactions such as central nervous system (CNS) haemorrhage (1%) and gastrointestinal (GI) haemorrhage (2%), in the context of severe thrombocytopenia, were reported in patients receiving decitabine. Cases of interstitial lung disease (ILD) (including pulmonary infiltrates, organising pneumonia and pulmonary fibrosis) without signs of infectious aetiology have been reported in patients receiving decitabine. Cases of myelosuppression, cardiac arrest, infections, hypersensitivity (anaphylaxis) and intracranial hemorrhage have been reported in patients receiving decitabine.

8.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Myelodysplastic Syndrome (MDS)

Option 1: In Patient (3-Day Dosing Regimen)

A Phase 3 (D-0007), randomized open-label, multicenter, controlled trial was conducted with DACOGEN plus supportive care vs. supportive care alone in 170 adult patients with MDS. 83 patients received DACOGEN intravenously infused at a dose of 15 mg/m^2 per body surface area 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. The median number of cycles completed was 3 for the DACOGEN and for Supportive Care treatment arms (range 1 to 9).

The most common adverse reactions in patients who received DACOGEN were: neutropenia (90%), thrombocytopenia (89%), anaemia (82%), fatigue (48%), pyrexia (53%), nausea (42%), cough (40%), petechiae (39%), constipation (35%), diarrhoea (34%), and hyperglycaemia (33%). Pyrexia, cough, headache, staphylococcal infection, and pneumonia occurred consistently throughout treatment. Fungal infections and bacteremia appeared as early events, as did febrile neutropenia, rigor and hyperbilirubinemia.

The overall incidence of death was similar (71% DACOGEN vs. 68% Supportive Care) for the two treatment arms during the study period or during long term follow-up. The major causes of death on study in both study arms were disease progression (MDS/AML) and infection. Fewer patients died on study in the DACOGEN arm (14%) than in the Supportive Care arm (22%). The situation was reversed in the long-term follow-up period (57% DACOGEN vs. 46% Supportive Care).

Serious adverse reactions (SARs) were experienced by 69% of the DACOGEN patients and 56% of the Supportive Care patients. SARs occurred most commonly in the SOC categories of *blood and lymphatic system disorders, general disorders and administrative sites conditions, infections and infestations and cardiac disorders.* The most common SARs in the DACOGEN arm that occurred in more than one patient and at an incidence numerically greater than in the Supportive Care arm were: febrile neutropenia (25%), pneumonia (17%), pyrexia (14%), and catheter-related infections (5%). The highest incidence of Grade 3 and/or Grade 4 SARs in the DACOGEN arm occurred with neutropenia (87%), thrombocytopenia (85%), febrile neutropenia (23%) and leukopenia (22%). In the first two treatment cycles, there was an increased risk of febrile neutropenia and increased requirements for transfusion which were not seen in later cycles.

Ten percent of patients discontinued due to toxicity. Adverse reactions for permanent discontinuation were due to thrombocytopenia (2%), neutropenia (1%), cardiopulmonary arrest (1%), pneumonia NOS (1%), lymphadenopathy (1%), elevated total bilirubin (1%), elevated SGPT (1%), Mycobacterium avium complex infection (1%), subarachnoid hemorrhage (1%), cardio-respiratory arrest (1%), increased blood bilirubin (1%), intracranial hemorrhage (1%), and abnormal liver function tests (1%).

Approximately one - third of patients receiving DACOGEN required dose delay or dose reduction. The adverse reactions most frequently resulting in permanent discontinuation were thrombocytopenia (2%), neutropenia (1%), cardiopulmonary arrest (1%), pneumonia NOS (1%), MAC infection (1%), subarachnoid hemorrhage (1%), lymphadenopathy (1%), elevated total bilirubin (1%), and elevated SGPT (1%). Adverse reactions leading to temporarily dose suspension were neutropenia (2%), pulmonary congestion (1%), atrial fibrillation (1%), central line infection (1%), and febrile neutropenia (1%); while adverse reaction leading to dose reduction were thrombocytopenia (4%), neutropenia (2%), tachycardia (1%), pharyngitis (1%), anemia (1%), lethargy (1%), edema (1%), and depression (1%).

Table 3 presents all adverse reactions occurring in at least 5% of patients in the DACOGEN group and at a rate greater than supportive care.

Table 3 – Adverse Reactions Occurring in ≥5% of Subjects in Myelodysplastic Syndromes (MDS) Study and at a Rate Greater than Supportive Care Study D-0007 with Option 1: In Patient (3-Day Dosing Regimen)

SOC Heading Preferred MedDRA Term	DACOGEN N = 83 (%)			Supportive Care N = 81 (%)		
	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)
Blood and Lymphatic System Disorders						
Neutropenia	8 (10)	64 (77)	75 (90)	20 (25)	20 (25)	58 (72)
Thrombocytopenia	18 (22)	52 (63)	74 (89)	22 (27)	13 (16)	64 (79)
Anemia	9 (11)	1 (1)	68 (82)	11 (14)	1 (1)	60 (74)
Febrile Neutropenia	14 (17)	5 (6)	24 (29)	3 (4)	0 (0)	5 (6)
Leukopenia	7 (8)	12 (14)	23 (28)	4 (5)	2 (2)	11 (14)
Lymphadenopathy	0 (0)	0 (0)	10 (12)	0 (0)	1 (1)	6 (7)
Thrombocythemia	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	1 (1)
Cardiac disorders						
Pulmonary oedema NOS	0 (0)	0 (0)	5 (6)	0 (0)	0 (0)	0 (0)
Eye disorders						
Vision blurred	1 (1)	0 (0)	5 (6)	0 (0)	0 (0)	0 (0)
Gastrointestinal Disorders						
Nausea	1 (1)	0 (0)	35 (42)	3 (4)	0 (0)	13 (16)
Constipation	2 (2)	0 (0)	29 (35)	1 (1)	0 (0)	11 (14)
Diarrhea	0 (0)	0 (0)	28 (34)	1 (1)	1 (1)	13 (16)
Vomiting	0 (0)	0 (0)	21 (25)	0 (0)	0 (0)	7 (9)
Abdominal pain NOS	2 (2)	0 (0)	12 (14)	3 (4)	0 (0)	5 (6)
Oral mucosal Petechiae	2 (2)	0 (0)	11 (13)	1 (1)	0 (0)	4 (5)
Stomatitis	0 (0)	0 (0)	10 (12)	0 (0)	0 (0)	5 (6)
Dyspepsia	1 (1)	0 (0)	10 (12)	0 (0)	0 (0)	1 (1)
Ascites	0 (0)	0 (0)	8 (10)	0 (0)	0 (0)	2 (2)
Gingival bleeding	1 (1)	0 (0)	7 (8)	0 (0)	0 (0)	5 (6)
Haemorrhoids	0 (0)	0 (0)	7 (8)	0 (0)	0 (0)	3 (4)
Loose stools	0 (0)	0 (0)	6 (7)	0 (0)	0 (0)	3 (4)
Tongue ulceration	0 (0)	0 (0)	6 (7)	0 (0)	0 (0)	2 (2)
Dysphagia	2 (2)	0 (0)	5 (6)	0 (0)	1 (1)	2 (2)
Oral soft tissue disorder NOS	0 (0)	0 (0)	5 (6)	0 (0)	0 (0)	1 (1)
Lip ulceration	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	3 (4)
Abdominal distension	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	1 (1)
Abdominal pain upper	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	1 (1)
Gastrooesophageal reflux disease	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	0 (0)
Glossodynia	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	0 (0)
General Disorders and Administration Site Conditions						
Pyrexia	4 (5)	1 (1)	44 (53)	0 (0)	1 (1)	23 (28)
Oedema peripheral	3 (4)	0 (0)	21 (25)	0 (0)	0 (0)	13 (16)

Table 3 – Adverse Reactions Occurring in ≥5% of Subjects in Myelodysplastic Syndromes (MDS) Study and at a Rate Greater than Supportive Care Study D-0007 with Option 1: In Patient (3-Day Dosing Regimen)

SOC Heading Preferred MedDRA Term	DACOGEN N = 83 (%)			Supportive Care N = 81 (%)		
	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)
Rigors	1 (1)	0 (0)	18 (22)	0 (0)	0 (0)	14 (17)
Oedema NOS	0 (0)	0 (0)	15 (18)	0 (0)	0 (0)	5 (6)
Pain NOS	3 (4)	0 (0)	11 (13)	0 (0)	0 (0)	5 (6)
Lethargy	2 (2)	1 (1)	10 (12)	0 (0)	0 (0)	3 (4)
Tenderness NOS	0 (0)	0 (0)	9 (11)	0 (0)	0 (0)	0 (0)
Fall	1 (1)	0 (0)	7 (8)	1 (1)	0 (0)	3 (4)
Chest discomfort	1 (1)	0 (0)	6 (7)	0 (0)	0 (0)	3 (4)
Intermittent pyrexia	0 (0)	0 (0)	5 (6)	1 (1)	0 (0)	3 (4)
Malaise	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	1 (1)
Crepitations NOS	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	1 (1)
Catheter site erythema	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	1 (1)
Catheter site pain	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	0 (0)
Injection site swelling	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	0 (0)
Hepatobiliary Disorders						
Hyperbilirubinaemia	4 (5)	1 (1)	12 (14)	0 (0)	0 (0)	4 (5)
Infections and Infestations						
Pneumonia NOS	11 (13)	2 (2)	18 (22)	6 (7)	2 (2)	11 (14)
Cellulitis	2 (2)	1 (1)	10 (12)	2 (2)	0 (0)	6 (7)
Candidal infection NOS	0 (0)	0 (0)	8 (10)	0 (0)	0 (0)	1 (1)
Catheter related infection	2 (2)	0 (0)	7 (8)	0 (0)	0 (0)	0 (0)
Urinary tract infection NOS	1 (1)	0 (0)	6 (7)	1 (1)	0 (0)	1 (1)
Staphylococcal infection	2 (2)	1 (1)	6 (7)	0 (0)	0 (0)	0 (0)
Oral candidiasis	0 (0)	0 (0)	5 (6)	0 (0)	0 (0)	2 (2)
Sinusitis NOS	0 (0)	0 (0)	4 (5)	1 (1)	0 (0)	2 (2)
Bacteraemia	2 (2)	0 (0)	4 (5)	0 (0)	0 (0)	0 (0)
Injury, poisoning and procedural complications						
Transfusion reaction	0 (0)	0 (0)	6 (7)	0 (0)	0 (0)	3 (4)
Abrasion NOS	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	1 (1)
Investigations						
Cardiac murmur NOS	0 (0)	0 (0)	13 (16)	0 (0)	0 (0)	9 (11)
Metabolism and nutrition disorders						
Appetite decreased NOS	0 (0)	0 (0)	13 (16)	1 (1)	1 (1)	12 (15)
Anorexia	0 (0)	0 (0)	13 (16)	1 (1)	0 (0)	8 (10)
Dehydration	1 (1)	0 (0)	5 (6)	1 (1)	0 (0)	4 (5)
Musculoskeletal and connective tissue disorders						
Arthralgia	3 (4)	0 (0)	17 (20)	0 (0)	0 (0)	8 (10)
Pain in limb	1 (1)	0 (0)	16 (19)	1 (1)	0 (0)	8 (10)

Table 3 – Adverse Reactions Occurring in ≥5% of Subjects in Myelodysplastic Syndromes (MDS) Study and at a Rate Greater than Supportive Care Study D-0007 with Option 1: In Patient (3-Day Dosing Regimen)

SOC Heading Preferred MedDRA Term	DACOGEN N = 83 (%)			Supportive Care N = 81 (%)		
	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)
Back pain	2 (2)	0 (0)	14 (17)	0 (0)	0 (0)	5 (6)
Chest wall pain	0 (0)	0 (0)	6 (7)	0 (0)	0 (0)	1 (1)
Musculoskeletal discomfort	0 (0)	0 (0)	5 (6)	0 (0)	0 (0)	0 (0)
Myalgia	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	1 (1)
Nervous system disorders						
Headache	2 (2)	0 (0)	23 (28)	0 (0)	0 (0)	11 (14)
Dizziness	0 (0)	0 (0)	15 (18)	2 (2)	0 (0)	10 (12)
Hypoaesthesia	0 (0)	0 (0)	9 (11)	0 (0)	0 (0)	1 (1)
Psychiatric disorders						
Insomnia	0 (0)	0 (0)	23 (28)	0 (0)	0 (0)	11 (14)
Confusional state	1 (1)	0 (0)	10 (12)	0 (0)	0 (0)	3 (4)
Anxiety	0 (0)	0 (0)	9 (11)	0 (0)	0 (0)	8 (10)
Renal and urinary disorders						
Dysuria	0 (0)	0 (0)	5 (6)	0 (0)	0 (0)	3 (4)
Urinary frequency	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	1 (1)
Respiratory, thoracic and mediastinal disorders						
Cough	0 (0)	0 (0)	33 (40)	0 (0)	0 (0)	25 (31)
Pharyngitis	2 (2)	0 (0)	13 (16)	0 (0)	0 (0)	6 (7)
Crackles lung	0 (0)	0 (0)	12 (14)	0 (0)	0 (0)	1 (1)
Breath sounds decreased	0 (0)	0 (0)	8 (10)	0 (0)	0 (0)	7 (9)
Hypoxia	5 (6)	0 (0)	8 (10)	1 (1)	1 (1)	4 (5)
Rales	0 (0)	0 (0)	7 (8)	0 (0)	0 (0)	2 (2)
Postnasal drip	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	2 (2)
Skin and subcutaneous tissue disorders						
Ecchymosis	1 (1)	0 (0)	18 (22)	0 (0)	0 (0)	12 (15)
Rash NOS	0 (0)	0 (0)	16 (19)	0 (0)	0 (0)	7 (9)
Erythema	0 (0)	0 (0)	12 (14)	0 (0)	0 (0)	5 (6)
Skin lesion NOS	0 (0)	0 (0)	9 (11)	0 (0)	0 (0)	3 (4)
Pruritis	0 (0)	0 (0)	9 (11)	0 (0)	0 (0)	2 (2)
Alopecia	0 (0)	0 (0)	7 (8)	0 (0)	0 (0)	1 (1)
Urticaria NOS	0 (0)	0 (0)	5 (6)	0 (0)	0 (0)	1 (1)
Swelling face	0 (0)	0 (0)	5 (6)	0 (0)	0 (0)	0 (0)
Vascular disorders						
Petechiae	2 (2)	0 (0)	32 (39)	1 (1)	0 (0)	13 (16)
Pallor	0 (0)	0 (0)	19 (23)	0 (0)	0 (0)	10 (12)
Hypotension NOS	1 (1)	0 (0)	5 (6)	0 (0)	1 (1)	4 (5)
Haematoma NOS	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	3 (4)

Table 4 presents serious adverse reactions in the myelodysplastic syndromes (MDS) D-0007 study not reported in previous table.

Table 4 – Other Serious Adverse Reactions In Myelodysplastic Syndromes (MDS) D-0007 Study with Option 1: In Patient (3-Day Dosing Regimen)

SOC Serious Adverse Event Preferred Term	DACOGEN (N = 83)			Supportive Care (N = 81)		
	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)
Blood and lymphatic system disorders						
Lymphadenopathy	0 (0)	0 (0)	2 (2)	0 (0)	0 (0)	0 (0)
Myelosuppression	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Splenomegaly	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Cardiac disorders						
Myocardial infarction	0 (0)	2 (2)	2 (2)	0 (0)	0 (0)	0 (0)
Cardiac failure congestive	1 (1)	0 (0)	1 (1)	0 (0)	1 (1)	1 (1)
Cardio–respiratory arrest	0 (0)	1 (1)	1 (1)	0 (0)	1 (1)	1 (1)
Cardiomyopathy NOS	0 (0)	1 (1)	1 (1)	0 (0)	1 (1)	1 (1)
Atrial fibrillation	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Cardiac failure NOS	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Supraventricular tachycardia	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Gastrointestinal disorders						
Gingival pain	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Upper gastrointestinal haemorrhage	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
General disorders and administrative site conditions						
Asthenia	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Mucosal inflammation NOS	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Catheter site haemorrhage	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Hepatobiliary disorders						
Cholecystitis NOS	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Infections and infestations						
Fungal infection NOS	0 (0)	1 (1)	2 (2)	0 (0)	0 (0)	0 (0)
Sepsis NOS	0 (0)	1 (1)	1 (1)	1 (1)	0 (0)	1 (1)
Upper respiratory tract infection NOS	0 (0)	0 (0)	1 (1)	1 (1)	0 (0)	1 (1)
Bronchopulmonary aspergillosis	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)

Table 4 – Other Serious Adverse Reactions In Myelodysplastic Syndromes (MDS) D-0007 Study with Option 1: In Patient (3-Day Dosing Regimen)

SOC Serious Adverse Event Preferred Term	DACOGEN (N = 83)			Supportive Care (N = 81)		
	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)
Peridiverticular abscess	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Respiratory tract infection NOS	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Lung infection pseudomonal	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Mycobacterium avium complex infection	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Injury, poisoning and procedural complications						
Post procedural pain	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Post procedural haemorrhage	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Nervous system disorders						
Intracranial haemorrhage NOS	1 (1)	1 (1)	3 (4)	0 (0)	0 (0)	0 (0)
Psychiatric disorders						
Mental status changes	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Renal and urinary disorders						
Renal failure	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Urethral haemorrhage	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Respiratory, thoracic and mediastinal disorders						
Dyspnoea	2 (2)	2 (2)	5 (6)	1 (1)	3 (3)	4 (5)
Hemoptysis	1 (1)	0 (0)	1 (1)	0 (0)	0 (0)	1 (1)
Lung infiltration NOS	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)
Pulmonary embolism	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Respiratory arrest	0 (0)	1 (1)	1 (1)	0 (0)	0 (0)	0 (0)
Pulmonary mass	0 (0)	0 (0)	1 (1)	0 (0)	0 (0)	0 (0)

More infections were reported in males and a greater incidence of febrile neutropenia was reported in females.

Adverse reactions that increased with age in patients receiving DACOGEN were anemia NOS, leukocytosis, CHF, tinnitus, blood creatinine increased, irregular heart rate, intracranial haemorrhage NOS, micturition disorder, contusion, ecchymosis, pallor and hypertension NOS.

No overall differences in safety or effectiveness were observed between patients 65 years and older as compared to younger subjects. However, in older individuals (75 years and older) catheter related infections (5% in patients 65 and older vs. 24% in patients 75 years and older) were reported more frequently. (See CLINICAL TRIALS).

Option 2: Out Patient (5-Day Dosing Regimen)

A phase 2, nonrandomized open-label, multicenter, single-arm study (DACO-020) in 99 adult patients with MDS was conducted in support of 5-Day dosing regimen. Patients received DACOGEN as a 20 mg/m^2 by surface area in 1-hour IV infusion once daily on Days 1 through 5 of a 4-week cycle in an outpatient setting. The median number of cycles administered was 5 (range 1 to 27).

The highest incidences of Grade 3 or Grade 4 adverse reactions were neutropenia (37%), thrombocytopenia (24%) and anemia (22%). Dose reduction was not allowed with this 5-Day dosing regimen. Seventy-eight percent of patients had dose delays, the median duration of this delay was 7 days and the largest percentage of delays was due to hematologic toxicities. Eight patients had fatal events due to infection and/or bleeding (seven of which occurred in the clinical setting of myelosuppression) that were considered at least possibly related to drug treatment. Nineteen of 99 patients (20%) permanently discontinued therapy for adverse-reactions.

Table 5 presents all adverse reactions occurring in at least 5% of subjects in Myelodysplastic Syndromes (MDS) DACO-020 study.

Table 5 – Adverse Reactions Occurring in ≥5% of Subjects in Myelodysplastic Syndromes (MDS) DACO-020 Study with Option 2: Out Patient (5-Day Dosing Regimen)

MedDRA System Organ Class MedDRA Preferred Term	DACOGEN (N = 99)		
	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
Blood and lymphatic system disorders			
Anaemia	15 (15.2)	7 (7.1)	31 (31)
Febrile neutropenia	13 (13.1)	4 (4.0)	20 (20)
Leukopenia	3 (3.0)	2 (2.0)	6 (6)
Neutropenia	7 (7.1)	30 (30.3)	38 (38)
Pancytopenia	1 (1.0)	4 (4.0)	5 (5)
Thrombocythaemia	1 (1.0)	0	5 (5)
Thrombocytopenia	6 (6.1)	18 (18.2)	27 (27)
Cardiac disorders			
Cardiac failure congestive	2 (2.0)	0	5 (5)
Tachycardia	0	0	8 (8)
Ear and labyrinth disorders			
Ear pain	0	0	6 (6)
Gastrointestinal disorders			
Abdominal pain	3 (3.0)	0	14 (14)
Abdominal pain upper	2 (2.0)	0	6 (6)
Constipation	0	0	30 (30)
Diarrhoea	0	0	28 (28)
Dyspepsia	1 (1.0)	0	10 (10)
Dysphagia	2 (2.0)	0	5 (5)
Gastrooesophageal reflux disease	0	0	5 (5)
Nausea	2 (2.0)	0	40 (40)
Oral pain	1 (1.0)	0	5 (5)
Stomatitis	3 (3.0)	0	11 (11)
Toothache	0	0	6 (6)

Table 5 – Adverse Reactions Occurring in ≥5% of Subjects in Myelodysplastic Syndromes (MDS) DACO-020 Study with Option 2: Out Patient (5-Day Dosing Regimen)

MedDRA System Organ Class MedDRA Preferred Term	DACOGEN (N = 99)		
	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
Vomiting	2 (2.0)	0	16 (16)
General disorders and administration site conditions			
Asthenia	5 (5.1)	0	15 (15)
Chest pain	1 (1.0)	0	6 (6)
Chills	0	0	16 (16)
Fatigue	11 (11.1)	1 (1.0)	46 (46)
Mucosal inflammation	0	0	9 (9)
Oedema	0	0	5 (5)
Oedema peripheral	1 (1.0)	0	27 (27)
Pain	0	0	5 (5)
Pyrexia	1 (1.0)	0	36 (36)
Infections and infestations			
Cellulitis	4 (4.0)	0	9 (9)
Oral candidiasis	1 (1.0)	0	6 (6)
Pneumonia	13 (13.1)	0	20 (20)
Sinusitis	0	0	6 (6)
Staphylococcal bacteraemia	7 (7.1)	0	8 (8)
Tooth abscess	0	0	5 (5)
Upper respiratory tract infection	1 (1.0)	0	10 (10)
Urinary tract infection	2 (2.0)	0	7 (7)
Injury, poisoning and procedural complications			
Contusion	0	0	9 (9)
Investigations			
Breath sounds abnormal	0	0	5 (5)
Weight decreased	0	0	9 (9)
Metabolism and nutrition disorders			
Anorexia	2 (2.0)	0	23 (23)
Decreased appetite	1 (1.0)	0	8 (8)
Dehydration	2 (2.0)	0	8 (8)
Hyperglycaemia	3 (3.0)	1 (1.0)	6 (6)
Hypokalaemia	2 (2.0)	0	12 (12)
Hypomagnesaemia	0	0	5 (5)
Musculoskeletal and connective tissue disorders			
Arthralgia	2 (2.0)	0	17 (17)
Back pain	3 (3.0)	0	18 (18)
Bone pain	1 (1.0)	0	6 (6)
Muscle spasms	0	0	7 (7)
Muscular weakness	2 (2.0)	0	5 (5)
Musculoskeletal pain	0	0	5 (5)
Myalgia	2 (2.0)	0	9 (9)
Pain in extremity	3 (3.0)	0	18 (18)
Nervous system disorders			

Table 5 – Adverse Reactions Occurring in ≥5% of Subjects in Myelodysplastic Syndromes (MDS) DACO-020 Study with Option 2: Out Patient (5-Day Dosing Regimen)

MedDRA System Organ Class MedDRA Preferred Term	DACOGEN (N = 99)		
	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
Dizziness	0	0	21 (21)
Headache	4 (4.0)	0	23 (23)
Psychiatric disorders			
Anxiety	1 (1.0)	0	9 (9)
Confusional state	0	0	8 (8)
Depression	0	0	9 (9)
Insomnia	0	0	14 (14)
Respiratory, thoracic and mediastinal disorders			
Cough	1 (1.0)	0	27 (27)
Dyspnoea	7 (7.1)	1 (1.0)	29 (29)
Epistaxis	3 (3.0)	0	13 (13)
Pharyngolaryngeal pain	1 (1.0)	0	8 (8)
Pleural effusion	0	0	5 (5)
Sinus congestion	0	0	5 (5)
Skin and subcutaneous tissue disorders			
Dry skin	0	0	8 (8)
Ecchymosis	0	0	9 (9)
Erythema	0	0	5 (5)
Night sweats	0	0	5 (5)
Petechiae	0	0	12 (12)
Pruritus	0	0	9 (9)
Rash	1 (1.0)	0	11 (11)
Skin lesion	1 (1.0)	0	5 (5)
Vascular disorders			
Hypertension	1 (1.0)	0	6 (6)
Hypotension	0	1 (1.0)	11 (11)

Table 6 presents serious adverse reactions in myelodysplastic syndromes (MDS) DACO-020 study by ≥ 2% of patients not reported in previous table.

Table 6 – Serious Adverse Reactions In Myelodysplastic Syndromes (MDS) Study Reported by ≥ 2% of Patients with Option 2: Out Patient (5-Day Dosing Regimen)

MedDRA System Organ Class MedDRA Preferred Term	DACOGEN (N = 99)		
	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
Cardiac disorders			
Myocardial infarction	0	1 (1.0)	2 (2.0)
General disorders and administration site conditions			
Disease progression	0	0	4 (4.0)
Infections and infestations			
Clostridial infection	2 (2.0)	0	3 (3.0)
Lung infection	2 (2.0)	0	2 (2.0)
Sepsis	1 (1.0)	1 (1.0)	4 (4.0)
Septic shock	0	1 (1.0)	2 (2.0)
Staphylococcal sepsis	2 (2.0)	0	2 (2.0)
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	2 (2.0)	1 (1.0)	4 (4.0)
Respiratory failure	1 (1.0)	0	2 (2.0)

The incidence of most adverse reactions was similar in both males and females.

In the blood and lymphatic system disorders SOC, patients ≥70 years of age had a higher incidence than patients 65 to 69 years old for adverse reactions of anemia (40.0% vs. 26.5%), neutropenia (48.6% vs. 32.7%), and thrombocytopenia (42.9% vs. 20.4%), but a lower incidence of febrile neutropenia (8.6% vs. 24.5%). Other adverse reactions having a ≥10% higher frequency in patients ≥70 years of age compared to patients aged 65-69 years include pneumonia (31.4% vs. 14.3%), dizziness (34.3% vs. 12.2%), confusional state (17.1% vs. 0%), and pollakiuria (11.4% vs. 0%).

8.3 Clinical Trial Adverse Reactions (Pediatrics)

There is no safety and efficacy data available from children. MDS occurs rarely in children.

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Option 1: In Patient (3-Day Dosing Regimen)

Clinically relevant abnormalities of routine hematological or biochemical laboratory values observed in the phase III clinical study (D-0007) are presented in Table 7:

Table 7 – Laboratory Abnormalities Observed in the Phase 3 Clinical Study (D-0007) with Option 1: In Patient (3-Day Dosing Regimen)

SOC Heading Preferred MedDRA Term	DACOGEN N = 83 (%)			Supportive Care N = 81 (%)		
	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)	Grade 3 N (%)	Grade 4 N (%)	All Grades N (%)
Neutropenia	8 (10)	64 (77)	75 (90)	20 (25)	20 (25)	58 (72)
Thrombocytopenia	18 (22)	52 (63)	74 (89)	22 (27)	13 (16)	64 (79)
Anemia	9 (11)	1 (1)	68 (82)	11 (14)	1 (1)	60 (74)
Leukopenia	7 (8)	12 (14)	23 (28)	4 (5)	2 (2)	11 (14)
Hyperbilirubinaemia	4 (5)	1 (1)	12 (14)	0 (0)	0 (0)	4 (5)
Blood alkaline phosphatase increased	0 (0)	0 (0)	9 (11)	0 (0)	0 (0)	7 (9)
Aspartate aminotransferase	1 (1)	0 (0)	8 (10)	0 (0)	0 (0)	7 (9)
Blood urea increased	0 (0)	0 (0)	8 (10)	0 (0)	0 (0)	1 (1)
Blood lactate dehydrogenase increased	0 (0)	0 (0)	7 (8)	0 (0)	0 (0)	5 (6)
Blood albumin decreased	0 (0)	0 (0)	6 (7)	0 (0)	0 (0)	0 (0)
Blood bicarbonate increased	0 (0)	0 (0)	5 (6)	0 (0)	0 (0)	1 (1)
Blood chloride decreased	0 (0)	0 (0)	5 (6)	0 (0)	0 (0)	1 (1)
Protein total decreased	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	3 (4)
Blood bicarbonate decreased	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	1 (1)
Blood bilirubin decreased	0 (0)	0 (0)	4 (5)	0 (0)	0 (0)	1 (1)
Hyperglycaemia NOS	7 (8)	0 (0)	27 (33)	1 (1)	0 (0)	16 (20)
Hypoalbuminaemia	2 (2)	0 (0)	20 (24)	1 (1)	0 (0)	14 (17)
Hypomagnesaemia	0 (0)	0 (0)	20 (24)	1 (1)	0 (0)	6 (7)
Hypokalaemia	2 (2)	0 (0)	18 (22)	4 (5)	0 (0)	10 (12)
Hyponatraemia	1 (1)	0 (0)	16 (19)	1 (1)	0 (0)	13 (16)
Hyperkalaemia	0 (0)	0 (0)	11 (13)	1 (1)	0 (0)	3 (4)

Option 2: Out Patient (5-Day Dosing Regimen)

Clinically relevant abnormalities of routine hematological or biochemical laboratory values observed in the phase II clinical study (DACO-020) are presented in Table 8:

Table 8 – Laboratory Abnormalities Observed In The Phase 2 Clinical Study (DACO-020) with Option 2: Out Patient (5-Day Dosing Regimen)

MedDRA System Organ Class MedDRA Preferred Term	DACOGEN (N = 99)		
	Grade 3 n (%)	Grade 4 n (%)	Total n (%)
Anaemia	15 (15.2)	7 (7.1)	31 (31)
Leukopenia	3 (3.0)	2 (2.0)	6 (6)
Neutropenia	7 (7.1)	30 (30.3)	38 (38)
Pancytopenia	1 (1.0)	4 (4.0)	5 (5)
Thrombocythaemia	1 (1.0)	0	5 (5)
Thrombocytopenia	6 (6.1)	18 (18.2)	27 (27)
Blood bilirubin increased	3 (3.0)	0	6 (6)
Hyperglycaemia	3 (3.0)	1 (1.0)	6 (6)
Hypokalaemia	2 (2.0)	0	12 (12)
Hypomagnesaemia	0	0	5 (5)

8.5 Post-Market Adverse Reactions

The following adverse reactions have been identified during post-approval 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. Based on the worldwide distribution of DACOGEN over the first 10 years of commercialization, the estimated exposure to decitabine is 119,471 treatment courses.

Cases of interstitial lung disease (including pulmonary infiltrates, organising pneumonia and pulmonary fibrosis), hypersensitivity including anaphylactic reaction and Sweet's Syndrome (acute febrile neutrophilic dermatosis) have been reported. Cases of enterocolitis have been reported, including events with a fatal outcome.

9 DRUG INTERACTIONS

9.1 Drug-Drug Interactions

Drug interaction studies with decitabine have not been conducted. There is the potential for a drug-drug interaction with other agents which are also activated by sequential phosphorylation (via intracellular phosphokinase activities) and/or metabolised by enzymes implicated in the inactivation of decitabine (e.g., cytidine deaminase). Therefore, caution should be exercised if these active substances are combined with decitabine. *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. Decitabine has been shown to be a weak inhibitor of P-glycoprotein (P-gp) mediated transport *in vitro* and is therefore also not expected to affect P-gp mediated transport of co-administered medicinal products.

9.2 Drug-Food Interactions

Interactions with food have not been established.

9.3 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.4 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 ACTION AND CLINICAL PHARMACOLOGY

10.1 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.

10.2 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.

In Vitro Antitumor Effects
In vitro, decitabine produced antiproliferative and differentiating effects in a panel of leukemic cell lines from murine and human origin, with IC_{50} values generally below 1µM. Similarly, decitabine decreased the proliferation of many solid tumor cell lines with IC50 values varying from the nM to the µM range. The differentiation effects were usually observed at concentrations that did not show clear cytotoxic effects. Also, in models of normal hematopoietic cell differentiation, decitabine reduced the growth and induced differentiation characteristic of normal hematopoietic cells without inducing cytotoxicity at concentrations of 10, 50 and 100 nM.

In Vivo Effects in Tumor Models
Decitabine showed dose-dependent antitumor activity in several mouse leukemia models as well as in a rat myeloid leukemia model, with a clear effect on survival at well-tolerated doses.

Decitabine displayed a synergistic interaction with histone deacetylase (HDAC) inhibitors, a class of agents that interfere with the deacetylation of histones and alter gene expression. However, antagonistic or conflicting results were obtained with drugs that block the cell cycle (hydroxyurea), or interfere with nucleoside synthetic pathways and DNA synthesis such as cytarabine. The latter interactions reflect the requirement for decitabine incorporation into DNA in cells progressing through the S-phase of the cell cycle.

10.3 Pharmacokinetics

In a single-arm, open-label, Phase 1 PK trial decitabine was administered to patients with MDS (≥30% blasts) at a dose of 15 mg/m^2 by surface area as a 3-hour infusion every 8 hours for 3 consecutive days of a 6-week cycle. Treatment length was to be 2 cycles, with PK measured in both cycles. Blood samples for PK analysis were collected from subjects (n=14) on days 1, 2, and 3 of cycle 1. There was no systemic accumulation of drug as determined by the day 3 to day 1 $AUC_{0-\infty}$ ratio of 0.99±0.29.

Table 9 – Mean (SD) Decitabine Pharmacokinetic Parameters Following a 15 mg/m^2 by Surface Area 3-hour Infusion (Day 1)

Dose	C_{max} (ng/mL)	T_{max} (h)	$t_{½}$ (h)	$AUC_{0-\infty}$ (ng-h/mL)	CL (L/h/m^2)	Vd_{ss} (L/m^2)
15 mg/m^2 3-hour infusion	73.8 (48.6) 66 [a]	2.49 (0.70) 28 [a]	0.62 (0.31) 49 [a]	163 (101) 62 [a]	125 (66.7) 53 [a]	71.8(62.7) 87 [a]

[a] Coefficient of variation (%)

Decitabine was administered intravenously at a dose of 20 mg/m^2 by surface area as a 1-hour IV infusion once daily for 5 days every 4 weeks in a study in MDS patients. Blood samples for PK analysis were collected from a subset of subjects (n=11) on day 5 of cycle 1. Samples were drawn before the start of the infusion, and at 30, 60 (immediately before the end of the infusion), 65, 75, 90 minutes and 2, 3, and 4 hours after the start of the infusion.

Table 10 – Mean (SD) Decitabine Pharmacokinetic Parameters Following a 20 mg/m^2 by Surface Area 1-hour Infusion

Dose*	C_{max} (ng/mL)	T_{max}[a] (h)	$t_{½}$ (h)	$AUC_{0-\infty}$ (ng-h/mL)	CL (L/h/m^2)	Vd_{ss} (L/m^2)
20 mg/m^2 1-hour infusion *	147 (71.6) 49 [b]	1.0 (0.5-1.08) 29[b]	0.54 (0.23) 43 [b]	115 (49.3) 43 [b]	210 (98.6) 47 [b]	89.7 (46.9) 52 [b]

* Day 5 of the first dosing cycle, once daily 1-h i.v. infusion (20 mg/m^2/day)
[a] Median (range)
[b] Coefficient of variation (%)

Distribution: A mass balance study in 4 subjects using a single 3-hour IV infusion of 20 mg ^{14}C-labelled compound demonstrated that decitabine has relatively slow distribution to the peripheral compartment with volume of distribution at steady state (Vd_{ss}) of 116 L.

Metabolism: Decitabine clearance is much higher than the normal hepatic blood flow (90 L/h). Decitabine clearance is much higher than the normal hepatic blood flow (90 L/h). The primary route of metabolism is likely thorough deamination by cytidine deaminase in the liver, kidney, intestinal epithelium and blood. Intracellularly, decitabine is activated through sequential phosphorylation via deoxycytidine kinase and other phosphokinase activities to the corresponding decitabine triphosphate which is then incorporated into DNA.

Elimination: The high total body clearance, low urinary excretion of unchanged drug in the urine, and high urinary excretion of metabolites indicate that decitabine is predominantly eliminated by metabolism.

Special Populations and Conditions

Pediatrics: There is no safety and efficacy data available from children. MDS occurs rarely in children.

Geriatrics: The pharmacokinetic parameters of decitabine were not shown to be dependent on age.

Ethnic origin: Most of the patients studied were Caucasian (95%).

Hepatic Impairment: The pharmacokinetics of decitabine have not been studied in patients with hepatic impairment. Results from a human mass-balance study and *in vitro* experiments indicated that the CYP enzymes are unlikely to be involved in the metabolism of decitabine.

Renal Impairment: The pharmacokinetics of decitabine have not been studied in patients with renal insufficiency. Results from a mass balance study in cancer patients with radioactive ^{14}C-decitabine showed that approximately 90% of the administered dose of decitabine is excreted in the urine with only 4.2% as unchanged drug. The major circulating metabolites are not known to be pharmacologically active.

11 STORAGE, STABILITY AND DISPOSAL

Storage

Store unopened vial between 15 and 30ºC.

Stability

After reconstitution: Unless used within 15 minutes of reconstitution, the diluted solution must be prepared using **cold** (2 to 8˚C) infusion fluids and should be stored at 2 to 8˚C for up to a maximum of 4 hours until administration. (See WARNINGS AND PRECAUTIONS, General).

Container Closure System	Storage Conditions (and In-use Storage Conditions, if applicable)	Shelf Life (and In-use Period, if applicable)
Reconstituted with 10 mL Sterile Water for Injection in Single-use clear colorless glass vial	Store at room temperature (15°C to 30°C)	15 minutes
Diluted to 0.1 – 1 mg/mL in Infusion Bag	Store at 2-8ºC	Up to 4 hours
	Infusion at room temperature	Up to 3 hours

Disposal

Any unused product or waste material should be disposed of in accordance with procedures for proper handling and disposal of cytotoxic medicinal products.

12 SPECIAL HANDLING INSTRUCTIONS

DACOGEN is a cytotoxic drug and caution should be exercised when handling and reconstituting. Procedures for proper handling of antineoplastic drugs should be applied. Skin contact should be avoided and protective gloves should be worn.

If reconstituted DACOGEN comes into contact with the skin, immediately and thoroughly wash with soap and water (see DOSAGE AND ADMINISTRATION, Reconstitution, WARNINGS AND PRECAUTIONS, General).

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

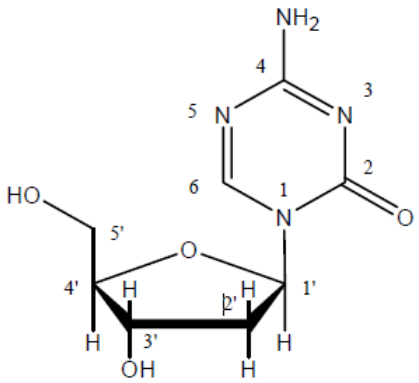
Proper/Common name: Decitabine

Chemical name: 4-Amino-1-(2-deoxy-β-D-erythro-pentofuranosyl)-1,3,5-triazin-2(1H)-one

Molecular formula and molecular mass: $C_8H_{12}N_4O_4$

228.21 daltons

Structural formula:



Physicochemical properties:

Decitabine is a fine, white, crystalline powder. Decitabine drug substance is sparingly soluble in water with a solubility of 8-12 mg/mL.

14 CLINICAL TRIALS

Myelodysplastic syndrome (MDS)
The clinical trial program for DACOGEN included a randomized controlled pivotal trial (D-0007), and a single arm Phase 2 study (DACO-020), involving 269 patients, conducted between 2001 and 2008.

These studies enrolled adult myelodysplastic syndromes (MDS) patients meeting French-American-British (FAB) classification criteria (1997) and International Prognostic Scoring System (IPSS) intermediate-1, intermediate-2 and high-risk prognostic scores (1997). Therefore, these trials included patients with blasts between 20 and 30% by the old FAB classification who are now considered AML by the World Health Organization classification (WHO 2008).

Patients with other progressive malignant disease; uncontrolled cardiac disease or uncontrolled congestive heart failure; creatinine values of >1.5 X upper limit of normal; total bilirubin of >1.5 X upper limit of normal, AST and ALT > 2.5 X upper limit of normal were excluded from these studies.

Option 1: In Patient (3-Day Dosing Regimen)

Phase 3 Trial (D-0007)

Supporting the 3-day dosing regimen, a randomized open-label, multicenter, controlled trial (D-0007) evaluated 170 MDS patients to compare the efficacy and safety of DACOGEN plus Supportive Care (SC) treatment arm to a Supportive Care (SC) only. Patients were randomized (1:1) to the DACOGEN arm to receive 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. Both treatment groups received standard medical care, i.e., blood and blood product transfusions, prophylactic antibiotics, and hematopoietic growth factors.

Eighty-nine (89) patients were randomized to DACOGEN therapy plus supportive care (only 83 received DACOGEN), and 81 to supportive care alone.

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 (2000); patients were required to be RBC and platelet transfusion independent during the time of response. Response criteria are given in Table 11:

Table 11 – Response Criteria for Phase 3 MDS Trial

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**

Patients in the DACOGEN and supportive care treatment arms had similar demographics, disease characteristics and baseline performance. No significant imbalances between the two treatment arms were present at baseline. Most patients were elderly (over 65 years of age), white males with *de novo* MDS that had been diagnosed at a median of approximately 30 weeks prior to start of study.

Table 12 – Summary of Patient Demographics and Baseline Disease Characteristics – Study D-0007 (MDS)

Parameter	DACOGEN N = 89	Supportive Care N = 81
Age (years)		
Mean (SD)	69 (10)	67 (10)
(Range: min-max)	(31–85)	(30–82)
Gender – n (%)		
Male	59 (66)	57 (70)
Female	30 (34)	24 (30)
Ethnic Origin – n (%)		
White	83 (93)	76 (94)
Black	4 (4)	2 (2)
Other	2 (2)	3 (4)
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)
WHO Performance Status – n (%)		
0	24 (27)	28 (35)
1	61 (69)	48 (59)
2	4 (4)	4 (5)
Missing Values	0 (0)	1 (1)
IPSS Classification – n (%)		
Intermediate–1	28 (31)	24 (30)
Intermediate–2	38 (43)	36 (44)
High Risk	23 (26)	21 (26)
Type of MDS – n (%)		
De novo	77 (87)	70 (86)
Secondary	12 (13)	11 (14)

AML=acute myeloid leukemia; CMML=chronic myelomonocytic leukemia; FAB =French-American-British classification; IPSS=International Prognostic Scoring System; MDS=myelodysplastic syndromes; RA=refractory anemia; RAEB=refractory anemia with excess blasts; RAEBt=refractory anemia with excess blasts in transformation; RARS=refractory anemia with ringed sideroblasts; SD=standard deviation

In the intention-to-treat (ITT) analysis, the overall response rate (ORR) in DACOGEN patients was superior, i.e.,17% (15/89) to that seen in the supportive care arm 0% (0/81), ($p < 0.001$). There were eight (8) patients with Complete Response and seven (7) with Partial Response. Responses were durable with a median duration of 288 days (range 116 – 388 days). Median time to response was 93 days (55–272 days) as shown in Table 13 below. The median cycle to respond was cycle 3.

Table 13 – Overall Adjudicated Response Rate (CR + PR), ITT Analysis Set – Study D-0007 (MDS)

Parameter	DACOGEN N = 89	Supportive Care N = 81	p-values†
Intention to Treat Analysis			
Overall Response Rate (CR + PR)	**15 (17%)**	**0 (0%)**	**< 0.001[1]**
95% CI Overall Response Rate	(9.8, 26.3)	(0, 4.5)	–
Complete Response (CR)	8 (9%)	0 (0%)	–
Partial Response (PR)	7 (8%)	0 (0%)	–
Median time to (CR + PR) response (days) (Range)	93 (55-272)	(0)	–
Median Duration of (CR + PR) response (days) (Range)	288 (116-388)	(0)	–

[1]From two-sided Fisher's Exact Test for equal Overall Response (CR+PR) Rate.

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

The other co-primary efficacy endpoint was time to AML or death. The date of progression to AML was taken from either the adjudicated (expert reviewer) or investigator data set, whichever provided the earliest diagnosis of AML. The time to AML or death in the ITT analysis did not reach statistical significance although DACOGEN patients had a trend toward longer median time to AML or death compared with patients treated with supportive care alone (12.1 vs. 7.8 months). Kaplan-Meier curves, with the DACOGEN treatment arm showed early separation in the ITT analysis and therefore suggest that progression to AML or death was delayed in the DACOGEN arm.

Table 14 – Time to AML or death* after 92 Events, ITT Analysis Set – Study D-0007 (MDS)

Parameter	DACOGEN N = 89	Supportive Care N = 81	p-value†
Number of events (%)	46 (52)	46 (57)	0.043[1], 0.160[2]
Median (95% CI) days	340 (285–407)	219 (148–379)	
Range days (min-max)[!]	24–624	7–432	

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

* Reflects analysis after 92 events. Patients crossing over or never receiving randomized treatment are censored

[!] From actual events only

[1] From two-sided Wilcoxon test for homogeneity of survival distributions

[2] From two-sided log-rank test for homogeneity of survival distributions

Subgroup analyses indicate that the Overall Response Rate (CR + PR) difference observed between the DACOGEN and Supportive Care treatment arms in the study population is robust and is maintained across IPSS risk groups, gender, age, FAB classifications (except RARS), type of MDS (de novo vs. secondary) and in patients with history of prior MDS treatment (prior therapy vs. treatment naïve).

A higher percentage of patients on the supportive care arm received erythropoietic growth factors compared with patients on the DACOGEN arm (41% vs. 20%).

Option 2: Out Patient (5-Day Dosing Regimen)

Phase 2 Study (DACO-020)

The outpatient use of DACOGEN in the treatment of patients with MDS was studied in a single-arm trial (DACO-020) with 99 patients. Patients received DACOGEN by intravenous infusion at a dose of 20 mg/m^2 by surface area over 1-hour daily, on days 1 to 5 of week 1 every, 4 weeks (1 cycle).

Table 15 – Summary of Patient Demographics and Baseline Disease Characteristics, ITT Analysis Set – Study DACO-020 (MDS)

Parameter	DACOGEN N = 99
Age (years)	
Mean (SD)	71(9)
(Range: min-max)	(34-87)
Gender – n (%)	
Male	71 (72)
Female	28 (28)
Race – n (%)	
White	86 (87)
Black	6 (6)
Asian	4 (4)
Other	3 (3)
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)
Type of MDS – n (%)	
De Novo	88 (89)
Secondary	11(11)

CMML=chronic myelomonocytic leukemia; FAB = French-American-British classification; IPSS=International Prognostic Scoring System; MDS=myelodysplastic syndromes; RA=refractory anemia; RAEB=refractory anemia with excess blasts; RAEBt=refractory anemia with excess blasts in transformation; RARS=refractory anemia with ringed sideroblasts; SD=standard deviation

In the ITT Analysis Set, the overall response rate (comprised of all patients with either a CR or PR) was 16% with a 95% CI of 9.5% to 24.9%. A complete response (CR) was achieved in 15% (15/99) patients, with 1% (1/99) patient achieving a partial response (PR). Responses were durable with a median duration of 443 days. The median number of days to achieve an initial response (CR or PR) was 162, with a range of 50 to 267 days. The overall improvement rate (comprised of all patients with either CR, PR, or Hematologic Improvement) was 43% with a 95% CI of 33.5% to 53.8%.

Table 16 – Patient Response on Study Using IWG-2000 Response Criteria, ITT Analysis Set – Study DACO-020 (MDS)

Best Response	Decitabine (N = 99) n (%)
Overall Response Rate (CR+PR)	**16 (16)**
--95% CI for Overall Response Rate	(9.5, 24.9)
Complete Remission (CR)	15 (15)
Partial Remission (PR)	1 (1)

CR= Complete Response; PR = Partial Response; CI = Confidence Interval

Results from subgroup analyses by baseline FAB, IPSS scores as well as baseline cytogenetic risk group, and baseline chromosomal abnormality showed overall responses were observed in all IPSS and FAB classifications except RAEB-t. However, one out of 6 RAEB-t patients experienced overall improvement. Amongst cytogenetic risks, none of the 12 patients with deletion of the 5q gene responded, however 4 (22%) of the 18 patients with chromosome 7 abnormality responded.

15 NON-CLINICAL TOXICOLOGY

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.

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 ≥ 0.3 mg/m^2. In females mated to males dosed with ≥ 0.3 mg/m^2 decitabine, pregnancy rate was reduced and preimplantation loss was significantly increased.

Decitabine had no effect on potassium currents in hERG-transfected HEK293 cells at concentrations up to 6.8 µg/mL and had no effect on cardiovascular or respiratory parameters in cynomolgus monkeys after a continuous IV infusion (1 hour) at a dose of 52.4 mg/kg (628.8 mg/m^2).

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PART III: PATIENT MEDICATION INFORMATION

PrDACOGEN®
Decitabine for Injection

Read this carefully before you start taking DACOGEN and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about DACOGEN.

Serious Warnings and Precautions for DACOGEN

DACOGEN should only be given by a healthcare professional. They must have experience and know how use drugs to treat cancer.

Side effects with DACOGEN can include:

- **Neutropenia:** This is a low level of white blood cells.
- **Thrombocytopenia**: This is a low level of platelets in the blood.
- DACOGEN can harm your unborn baby if you take it while you are pregnant.

What is DACOGEN used for?

DACOGEN is used to treat adults with Myelodysplastic Syndromes (MDS). These are blood disorders. It is used when MDS:

- was untreated or previously treated with chemotherapy
- can't be treated with stem cell transplant

How does DACOGEN work?

DACOGEN blocks the action of certain enzymes that are involved in the division of cancer cells. By blocking this action, it slows their growth and the progression of the disease. DACOGEN also kills cancer cells.

What are the ingredients in DACOGEN?

Medicinal ingredients: Decitabine
Non-medicinal ingredients: Potassium dihydrogen phosphate, sodium hydroxide

DACOGEN comes in the following dosage forms:

Glass vial of 50 mg lyophilized powder

Do not use DACOGEN if:

- You are allergic to it or to any of the other ingredients.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take DACOGEN. Talk about any health conditions or problems you may have, including if you have:

- heart failure, disease or disorder
- a bleeding disorder
- a low blood cell count for platelets, red or white blood cells
- an infection or flu-like symptoms
- liver disease
- a serious kidney disorder
- lung disease or pneumonia

Other warnings you should know about:

Fertility, pregnancy, females of child-bearing potential, breast-feeding and male patients
Tell your doctor if you:

- are pregnant
- think you might be pregnant
- are planning to have a baby
- are breast-feeding

DACOGEN can affect your ability to have a baby. This occurs in both women and men.

Your doctor will speak with you about the risks of DACOGEN if you are pregnant, or planning to become pregnant or breast-feed.

- You should not use DACOGEN if you are pregnant as it may harm your baby. Tell your doctor immediately if you become pregnant during treatment with DACOGEN.
- Women must use effective contraception during treatment. It is unknown when it is safe for women to become pregnant after treatment has stopped.
- Talk to your doctor if you wish to freeze your eggs before starting treatment.
- Do not breast-feed if you are using DACOGEN. This is because it is not known if the medicine passes into the mother's milk.

Men should not father a child while using DACOGEN.

- Men should use effective contraception during treatment and for 3 months after treatment has stopped.
- Talk to your doctor if you wish to conserve your sperm before starting treatment.

Driving and Using Machines: While using DACOGEN you may feel weak, tired, dizzy, or confused. You may have blurred vision. Before driving a vehicle or using machinery wait to see how you feel after taking DACOGEN.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How will I receive DACOGEN?
Only a doctor who has experience treating cancer should treat you with this drug.

Healthcare professionals must avoid skin contact with DACOGEN. They should wear gloves. They must follow procedures for working with and disposing of cytotoxic drugs. Medicine for nausea and vomiting may be needed. You and your doctor can decide if you need this or not.

DACOGEN comes as a powder. It gets mixed with a diluent then further mixed with fluids. It is only for intravenous use. The solution should appear clear and without any particles. The proper preparation, administration and mixing of DACOGEN will be done by your healthcare professional. They will also store and dispose of the product.

There are two treatment options for DACOGEN. It is important to make sure the Intravenous (IV) runs at the correct rate.

Treatment option 1: **In Patient (3-Day dosing regimen)**
The usual dose is 15 mg/m^2 given to you by intravenous infusion (IV). **It is given over three hours**.

DACOGEN is given in cycles. It is given on this dosing schedule:
- Three times a day for 3 days.
- Your doctor will tell you when to start the next cycle.
- This cycle is repeated every 6 weeks.

Treatment option 2: **Out Patient (5-Day dosing regimen)**
The dose is 20 mg/m^2 given to you by intravenous infusion (IV). **It is given over one hour**.

DACOGEN is given in cycles. It is given on this dosing schedule:
- Once a day for 5 days.
- This cycle is repeated every 4 weeks.

For both options you will usually receive at least 4 cycles. Treatment may be continued for more cycles if you:
- show response,
- continue to benefit,
- as long as you are feeling well and your disease has not gotten worse.

Your doctor may delay your dose and change the total number of cycles. It will depend on how you respond to the treatment or if you have side effects.

Adult dose:
Your doctor will determine your dose of DACOGEN. This will depend on your body size.
The usual dose is in mg/m^2. That means the number of mg per square metre of body surface.

Overdose:
This medicine will be given by your doctor or nurse. In the unlikely event that you are given too much your doctor will check you for side effects and manage them accordingly.

If you think you have been given too much DACOGEN, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed appointment for receiving your medicine:
If you miss an appointment, make another one as soon as possible. For this medicine to be as effective as possible, you must follow the dosing schedule.

What are possible side effects from using DACOGEN?
These are not all the possible side effects you may feel when taking DACOGEN. If you experience any side effects not listed here, contact your healthcare professional.

- constipation, nausea, vomiting, diarrhea
- loss of appetite, mouth or tongue ulcer
- headache, dizziness, fatigue
- blurred vision
- redness, swelling, pain where the needle enters your skin during injection
- rash, skin redness, itching
- nose bleeds, sore or runny nose, sore sinuses
- chills

DACOGEN can cause abnormal blood test results including liver and kidney blood tests. You should have a blood test before each cycle of DACOGEN and whenever needed based on your condition. Your doctor will decide when to perform blood tests and will interpret the results. You may need antibiotics, growth factor support or a blood transfusion.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
VERY COMMON **Anemia (low level of red blood cells):** feeling weak, tired or short of breath. Fatigue, loss of energy, or looking pale.		X	
Infections such as sepsis, septic shock, caused by bacteria, virus or fungi: fever (high temperature), chills, and shivering. Sore throat, cough, runny nose, sore sinuses. Fast heart rate and pulse (tachycardia). Short of breath, and rapid breathing. Red and swollen IV site. Extreme weakness. Changes in mental ability.		X	
Neutropenia or Leukopenia (low level of white blood cells): Fever or infection, fatigue, aches and pains, and flu-like symptoms.		X	
Febrile neutropenia (fever with low level of white blood cells): fever, chills. Sores in mouth, toothache. Abdominal pain. Pain near anus or when urinating. Urinating often. Cough, feeling short of breath. Any redness, swelling or pain of skin. Unusual vaginal discharge or itching. Diarrhea.		X	
Hyperglycemia (high blood sugar): extreme thirst, frequent urination, extreme hunger, weakness, blurred vision.		X	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Thrombocytopenia (low level of blood platelets. These help the blood to clot): Tiny red or purple spots on the skin or inside the mouth (petechiae). Bruising or bleeding for longer than usual if you hurt yourself or more easily. Bleeding from gums or nose. Blood in urine or stool. Fatigue and weakness.		X	
Cellulitis (infection of skin): redness, swelling, pain and tenderness, warm to touch.		X	
Edema (swelling): unusual swelling of the arms and legs.	X		
COMMON **CNS hemorrhage (bleeding in the brain):** sudden severe headache. Weak, numb or cannot move arms, legs or face. Difficulty talking. Fainting or passing out. Dizziness, blurred vision, seizure (fit).			X
Liver disorder or increased liver enzymes: Jaundice. Yellow skin or eyes, dark urine, abdominal pain or swelling, nausea, vomiting. Loss of appetite.		X	
Genito-urinary hemorrhage (bleeding in the bladder or urinary tract): including blood in the urine.		X	
GI hemorrhage (bleeding in the stomach or bowels): severe abdominal pain or swelling. Vomit blood, black or bloody bowel movement, diarrhea. Feel dizzy or weak, loss of consciousness. Shortness of breath.			X

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Pneumonia (infection of the lungs): chest pain or shortness of breath. Difficult and painful breathing, cough, wheezing, or fever.			X
Change in mental status: Sad mood that does not go away. Confusion. Anxiety. Difficulty sleeping.	X		
Hypotension (low blood pressure): dizziness, fainting, lightheadedness.		X	
Hypertension (high blood pressure): Headaches, vision disorder, nausea and vomiting.		X	
Pulmonary hemorrhage (bleeding in the lungs) or edema (fluid in the lungs): Coughing up blood, shortness of breath, blue tinged lips, blood-tinged froth.			X
Urinary tract infection: pain and/or burning when urinating. Blood in the urine. Increased urge to urinate. Cloudy urine.		X	
UNCOMMON **Sweet's syndrome**, or **acute febrile neutrophilic dermatosis (a rare skin condition):** Sore red spots or blisters on the head, neck, legs, and arms. They are particularly on the back of the hands and fingers. Fever, joint pain, and sore eyes.		X	
UNKNOWN FREQUENCY **Anaphylaxis (allergic reactions):** Rash, hives, swelling of the face, lips, tongue or throat, difficulty swallowing or breathing.		X	

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
Interstitial lung disease (diseases that inflame or scar lung tissue): sudden shortness of breath, tiredness, dry cough. Generally feeling unwell.			X

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Your doctor, nurse or pharmacist store, prepare and dispose DACOGEN for you.

Do not use this medicine after the expiry date. It is stated on the carton and vial labels.

Store unopened vial between 15 and 30°C.
If you want more information about DACOGEN:
- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (http://hc-sc.gc.ca/index-eng.php); the company's website www.taihopharma.ca, or by calling 1-844-648-2446.

This leaflet was prepared by Otsuka Pharmaceutical Co., Ltd.

Last Revised: December 17, 2019