DACOGEN

FULL PRESCRIBING INFORMATION

1. NAME OF THE MEDICINAL PRODUCT

DACOGEN 50 mg powder for concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial of powder for concentrate for solution for infusion contains 50 mg decitabine.

After reconstitution with 10 ml of water for injections, each ml of concentrate contains 5 mg of decitabine.

Excipients with known effect
Each vial contains 0.29 mmol sodium (E524).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for infusion).

White to almost white lyophilized powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

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

DACOGEN is indicated for the treatment of adult patients with newly diagnosed de novo or secondary acute myeloid leukaemia (AML), according to the World Health Organisation (WHO) classification, who are not candidates for standard induction chemotherapy.

4.2. Posology and Method of Administration

DACOGEN administration must be initiated under the supervision of physicians experienced in the use of chemotherapeutic agents.

Posology

There are 2 regimens recommended for DACOGEN administration. A 5-Day dosing regimen in the treatment of AML, and a 3-Day or 5-Day dosing regimen in the treatment of MDS.

Pre-medication for the prevention of nausea and vomiting is not routinely recommended but may be administered if required

MDS

There are two regimens for Dacogen administration for MDS. 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.

In the AML Phase 3 study, the median time to response (complete remission [CR] or CR with incomplete platelet recovery [CRp]) was 4.3 months. In MDS, the median time to response (CR+PR) in the Phase 2 MDS studies with the 5-Day dosing regimen was 3.5 cycles. In the Phase 3 MDS study with the 3-Day dosing regimen, the median time to response was 3 cycles. Treatment may be continued as long as the patient shows response, continues to benefit or exhibits stable disease, i.e., in the absence of overt progression.

If after 4 cycles, the patient's hematological values (e.g., platelet counts or absolute neutrophil count [ANC]), 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.

4.2.1 Treatment Regimen – Option 1

Dacogen is administered at a dose of 15 mg/m^2 body surface by continuous intravenous infusion over 3 hours repeated every 8 hours for 3 days. This cycle should be repeated every 6 weeks Patients may be premedicated with standard anti-emetic therapy.

4.2.2 Treatment Regimen – Option 2

Dacogen is administered at a dose of 20 mg/m^2 by continuous intravenous infusion over 1 hour repeated daily for 5 days .This cycle should be repeated every 4 weeks. Patients may be premedicated with standard anti-emetic therapy.

4.2.3 Patients with Non-hematologic Toxicity

Following treatment with either DACOGEN regimen, if the following non-hematological toxicities occur, the next cycle of DACOGEN therapy should be withheld until levels return to within the normal range or baseline:

-Serum creatinine greater than or equal to 2 mg/dL. Serum glutamate pyruvate transaminase (SGPT) or alanine aminotransferase (ALT) or, total bilirubin greater than or equal to 2 times the upper limit of normal (ULN).

-Active viral or bacterial infection that is not controlled by concomitant anti-infective therapy.

AML

In a treatment cycle, Dacogen is administered at a dose of 20 mg/m^2 body surface area by intravenous infusion over 1 hour repeated daily for 5 consecutive days (i.e., a total of 5 doses per treatment cycle). The total daily dose must not exceed 20 mg/m^2 and the total dose per treatment cycle must not exceed 100 mg/m^2. If a dose is missed, treatment should be resumed as soon as possible.

The cycle should be repeated every 4 weeks depending on the patient's clinical response and observed toxicity. It is recommended that patients be treated for a minimum of 4 cycles; however, a complete or partial remission may take longer than 4 cycles to be obtained. Treatment may be continued as long as the patient shows response, continues to benefit or exhibits stable disease, i.e., in the absence of overt progression.

If after 4 cycles, the patient’s haematological 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.

Management of myelosuppression and associated complications

Myelosuppression and adverse events related to myelosuppression (thrombocytopenia, anaemia, neutropenia, and febrile neutropenia) are common in both treated and untreated patients with AML and MDS.

Complications of myelosuppression include infections and bleeding. Treatment may be modified in patients experiencing myelosuppression and associated complications as described below:

In AML

Treatment may be delayed at the discretion of the treating physician, if the patient experiences myelosuppression-associated complications, such as those described below:

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

Treatment with DACOGEN may be resumed once these conditions have improved or have been stabilized with adequate treatment (anti-infective therapy, transfusions, or growth factors).

In clinical studies, approximately one-third of patients receiving DACOGEN required a dose-delay. Dose reduction is not recommended.

In MDS

3-Day Dosing Regimen

Dose Regimen Modifications in the First 3 Cycles

During the first cycles of treatment, Grade 3-4 cytopenias are common and may not represent progression of MDS. Pre-treatment cytopenias may not improve until after Cycle 3.

For the first 3 cycles, to optimize patient benefit in the setting of moderate neutropenia (absolute neutrophil count < 1000/µL), all attempts should be made to maintain full dose treatment at the standard treatment cycle interval. Concomitant antimicrobial prophylaxis as per institutional guidelines can be administered until recovery of granulocytes to above 500/µL. Clinicians should also consider the need for early administration of growth factors during this time for the prevention or treatment of infections in patients with MDS.

Similarly, to optimize patient benefit in the setting of moderate thrombocytopenia (platelet count <25,000/µL), all attempts should be made to maintain full dose treatment at the standard treatment cycle interval with concomitant administration of platelet transfusions in case of bleeding events.

Dose Modifications After Cycle 3

If hematologic recovery (absolute neutrophil count ≥ 1,000/µL and platelets ≥ 50,000/µL) from a previous Dacogen treatment cycle with persistent cytopenia(s) being considered related to drug administration, requires more than 6 weeks, then the next cycle of Dacogen therapy should be delayed and dosing reduced by the algorithm below. All dose reductions that occur should remain in effect for the duration of the chemotherapy; there should be no dose re-escalation.

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

• Recovery requiring more than 8, but less than 10 weeks – the Dacogen dose should be delayed up to 2 more weeks and the dose reduced to 11 mg/m^2 every 8 hours (33 mg/m^2/day, 99 mg/m^2/cycle) upon restarting therapy, then maintained in subsequent cycles as clinically indicated.

• Recovery requiring more than 10 weeks – Patient should be discontinued from the treatment of the drug and assessed for disease progression (by bone marrow aspirate) within 7 days after the end of 10 weeks. However, for patients who have been treated for at least 6 cycles, and who continue to derive benefit from the therapy, a prolonged delay beyond 10 weeks can be allowed, in the absence of progression at the direction of the treating physician.

5-Day Dosing Regimen

Dose reduction is not recommended in this clinical setting to optimize

patient benefit, dose should be delayed as follows:

Dose Regimen Modifications in the first 3 Cycles

During the first cycles of treatment, Grade 3 and - 4 cytopenias are common and may not represent progression of MDS. Pre-treatment cytopenias may not improve until after Cycle 3.

For the first 3 cycles, to optimize patient benefit in the setting of moderate neutropenia (absolute neutrophil count < 1000/µL), all attempts should be made to maintain full dose treatment at the standard treatment cycle interval. Concomitant antimicrobial prophylaxis as per institutional guidelines can be administered until recovery of granulocytes to above 500/µL. Clinicians should also consider the need for early administration of growth factors during this time for the prevention or treatment of infections in patients with MDS.

Similarly, to optimize patient benefit in the setting of moderate thrombocytopenia (platelet count <25,000/µL), all attempts should be made to maintain full dose treatment at the standard treatment cycle interval with concomitant administration of platelet transfusions in case of bleeding events.

Dose Regimen Modifications after Cycle 3

Dose should be delayed in case of the following toxicities considered to be at least possibly related to the treatment:

-Severe myelosuppression-associated complications (infections not resolving with adequate anti-infective therapy, bleeding not resolving with adequate treatment).

-Prolonged myelosuppression defined as a hypocellular marrow (5% or less cellularity) without evidence of disease progression for 6 weeks or more after the start of a course of therapy.

If recovery (absolute neutrophil count >1,000/µL and platelets >50,000/µL) requires more than 8 weeks, the patient should be discontinued from the treatment of drug and assessed for disease progression (by bone marrow aspirate) within 7 days after the end of 8 weeks. For patients who have been treated for at least 6 cycles, and who continue to derive benefit from the therapy, a prolonged delay beyond 8 weeks can be allowed, in the absence of progression, at the discretion of the treating physician.

Special Populations:

Paediatric population

The safety and efficacy of Dacogen in children aged < 18 years have not yet been established. No data are available.

Hepatic impairment

Studies in patients with hepatic impairment have not been conducted. The need for dose adjustment in patients with hepatic impairment has not been evaluated. Dacogen should be used with caution in these

patients. If worsening hepatic function occurs, patients should be carefully monitored (see sections 4.4 and 5.2).

Renal impairment

Studies in patients with renal impairment have not been conducted. Dacogen should be used with caution in these patients.

The need for dose adjustment in patients with renal impairment has not been evaluated (see section 4.4 and 5.2).

The use of Dacogen in patients with renal or hepatic impairment has not been established. Caution should be exercised in the administration of Dacogen to patients with hepatic or renal impairmentand patients should be monitored closely for signs of toxicity.

Geriatric Use

Of the total number of MDS patients exposed to Dacogen in the controlled clinical trial, 61 of 83 patients were age 65 and over, while 21 of 83 patients were age 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Method of Administration

DACOGEN is administered by intravenous infusion. A central venous catheter is not required. For instructions on reconstitution and dilution of the medicinal product before administration, see Section 6.6.

4.3 CONTRAINDICATIONS

- Hypersensitivity to decitabine or to any of the excipients, listed in section 6.1.

- Breast feeding (see warnings and precautions)

4.4 Special Warnings and Special Precautions for Use

Myelosuppresion

Myelosuppression and complications of myelosuppression, including infections and bleeding that occur in patients with MDS or AML may be exacerbated with DACOGEN treatment. Therefore patients are at increased risk for severe infections (due to any pathogen such as bacterial, fungal and viral), with potentially fatal outcome (see section 4.8). Patients should be monitored for signs and symptoms of infection and treated promptly.

In AML clinical studies, the majority of patients had baseline Grade 3/4 myelosuppression. In patients with baseline Grade 2 abnormalities, worsening of myelosuppression was seen in most patients and more

frequently than in patients with baseline Grade 1 or 0 abnormalities. Myelosuppression caused by DACOGEN is reversible.

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, treatment with DACOGEN may be interrupted and/or supportive measures instituted (see sections 4.2 and 4.8).

In MDS studies, 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.

Embryo-Fetal Toxicity

In MDS 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* Preclinical Safety Data *(5.31)]*. 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 Fertility, Pregnancy and lactation 4.6)]*.

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 section 4.8).

Hepatic impairment

Use in patients with hepatic impairment has not been established. Caution should be exercised in the administration of Dacogen to patients with hepatic impairment

and in patients who develop signs or symptoms of hepatic impairment. Liver function tests should be performed prior to initiation of therapy and prior to each treatment cycle, and as clinically indicated (see sections 4.2 and 5.2).

Renal impairment

Use in patients with severe renal impairment has not been studied. Caution should be exercised in the administration of DACOGEN to patients with severe renal impairment (Creatinine Clearance [CrCl] <30 ml/min) and these patients should be monitored closely (see section 4.2). Renal function tests should be performed prior to initiation of therapy and prior to each treatment cycle, and as clinically indicated (see section 4.2).

Cardiac disease

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. Cases of cardiomyopathy with cardiac decompensation, in some cases reversible after treatment discontinuation, dose reduction or corrective treatment, have been reported in the postmarketing setting. Patients, especially those with cardiac disease history, should be monitored for signs and symptoms of heart failure.

Differentiation syndrome

Cases of differentiation syndrome (also known as retinoic acid syndrome) have been reported in patients receiving decitabine. Differentiation syndrome may be fatal (see section 4.8). Treatment with high-dose IV corticosteroids and haemodynamic monitoring should be considered at first onset of symptoms or signs suggestive of differentiation syndrome. Temporary discontinuation of Dacogen should be considered until resolution of symptoms and if resumed, caution is advised.

Excipients

This medicine contains 0.5 mmol potassium per vial. After reconstitution and dilution of the solution for intravenous infusion, this medicine contains less than 1 mmol (39 mg) of potassium per dose, i.e. essentially 'potassium- free'

This medicine contains 0.29 mmol sodium per vial. After reconstitution and dilution of the solution for intravenous infusion, this medicine contains between 13.8 mg-138 mg (0.6-6 mmol) sodium per dose (depending on the infusion fluid for dilution), equivalent to 0.7-7% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

4.5 Interactions with Other Medicinal Products and Other Forms of Interaction

No formal clinical drug interaction studies with decitabine have 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 metabolized by enzymes implicated in the inactivation of decitabine (e.g., cytidine deaminase). Therefore, caution should be exercised if these active substances are combined with DACOGEN.

Impact of co-administered medicinal products on decitabine

Cytochrome (CYP) 450-mediated metabolic interactions are not anticipated as decitabine metabolism is not mediated by this system but by oxidative deamination.

Impact of decitabine on co-administered medicinal products

Given its low *in vitro* plasma protein binding (<1%), decitabine is unlikely to displace co-administered medicinal products from their plasma protein binding.

Decitabine has been shown to be a weak inhibitor of P-gp mediated transport *in vitro* and is therefore also not expected to affect P-gp mediated transport of co-administered medicinal products (see Section 5.2).

4.6 Fertility, Pregnancy and lactation

The use of Dacogen with hormonal contraceptives has not been studied.

Women of childbearing potential/Contraception in men and women

DACOGEN can cause fetal harm when administered to pregnant women. Due to the genotoxic potential of decitabine (see section 5.3), women of childbearing potential must use effective contraceptive measures and avoid becoming pregnant while being treated with Dacogen and for 6 months following completion of treatment Men should use effective contraceptive measures and be advised to not father a child while receiving Dacogen, and for 3 months following completion of treatment (see section 5.3).

Pregnancy

There are no adequate data on the use of Dacogen in pregnant women. Studies have shown that decitabine is teratogenic in rats and mice (see section 5.3). The potential risk for humans is unknown. Based on results from animal studies and its mechanism of action, Dacogen should not be used during pregnancy and in women of childbearing potential not using effective contraception. A pregnancy test should be performed on all women of childbearing potential before treatment is started. If Dacogen is used during pregnancy, or if a patient becomes pregnant while receiving this medicinal product, the patient should be apprised of the potential hazard to the foetus.

Breast-feeding

It is not known whether decitabine or its metabolites are excreted in breast milk. Dacogen is contraindicated during breast-feeding; therefore, if treatment with this medicine is required, breast-feeding must be discontinued (see section 4.3).

Fertility

No human data on the effect of decitabine on fertility are available. In non-clinical animal studies, decitabine alters male fertility and is mutagenic. Because of the possibility of infertility as a consequence of Dacogen therapy, men should seek advice on conservation of sperm and female patients of childbearing potential should seek consultation regarding oocyte cryopreservation prior to initiation of treatment with Dacogen.

4.7 Effects on Ability to Drive and Use Machines

DACOGEN has moderate influence on the ability to drive and use machines. Patients should be advised that they may experience undesirable effects such as anemia during treatment. Therefore, caution should be recommended when driving a car or operating machines.

4.8 Undesirable Effects

MDS

Clinical Studies 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.*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.

Discussion of Adverse Reactions Information

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).

Table 1 presents all adverse events regardless of causality occurring in at least 5% of patients in the Dacogen group and at a rate greater than supportive care.

Table 1 Adverse Events 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)
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)
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 intravenous, infused over one hour daily for 5 consecutive days of a 4 week cycle. Table 2 presents all adverse events regardless of causality occurring in at least 5% of patients.

Table 2 Adverse Events 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)
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)
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 Events 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.

Post marketing Experience

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.

- Sweet's syndrome (acute febrile neutrophilic dermatosis).
- Differentiation syndrome

AML

Summary of the safety profile

The most common adverse drug reactions (≥ 35%) reported-are pyrexia, anemia and thrombocytopenia.

The most common Grade 3/4 adverse drug reactions (≥ 20%) included pneumonia, thrombocytopenia, neutropenia, febrile neutropenia and anaemia.

In clinical studies, 30% of patients treated with Dacogen and 25% of patients treated in the comparator arm had adverse events with an outcome of death during treatment or within 30 days after the last dose of study drug.

In the Dacogen treatment group, there was a higher incidence of treatment discontinuation due to adverse events in women compared to men (43% versus 32%).

Tabulated list of adverse drug reactions

Adverse drug reactions reported in 293 AML patients treated with Dacogen are summarised in Table 3. The following table reflects data from AML clinical studies and from post-marketing experience. The adverse drug reactions are listed by frequency category. Frequency categories are defined as follows: Very common

(≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000), not known (frequency cannot be estimated from the available data).

Within each frequency grouping, adverse drug reactions are presented in order of decreasing seriousness.

Table 3: Adverse Drug Reactions Identified with DACOGEN [2]

System Organ Class	Frequency (all Grades)	Adverse Drug Reaction	Frequency	
			All Grades[a] (%)	Grades 3-4[a] (%)
Infections and infestations	Very common	pneumonia*	24	20
		urinary tract infection*	15	7
		All other infections (viral, bacterial, fungal)*[b,c,d]	63	39
	Common	septic shock*	6	4
		sepsis*	9	8
		sinusitis	3	1
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Not known	differentiation syndrome	Not known	Not known
Blood and lymphatic disorders	Very common	febrile neutropenia*	34	32
		neutropenia*	32	30
		thrombocytopenia[b,e]*	41	38
		anaemia	38	31
		leukopenia	20	18
	Uncommon	Pancytopenia*	<1	<1
Immune system disorders	Common	Hypersensitivity including anaphylactic reaction [e,f]	1	<1
Metabolism and nutrition disorders	Very common	hyperglycaemia	13	3
Metabolism and nutrition disorders	Very common	hyperglycaemia	13	3
Nervous system disorders	Very common	headache	16	1
Cardiac disorders	Uncommon	cardiomyopathy	< 1	< 1
Respiratory, thoracic and mediastinal disorders	Very common	epistaxis	14	2
	Not known	interstitial lung disease	Not known	Not known
Gastrointestinal	Very	diarrhoea	31	2

disorders	common	vomiting	18	1
		nausea	33	<1
	Common	stomatitis	7	1
	Not known	Enterocolitis, including neutropaenic colitis, caecitis*	Not known	Not known
Hepatobiliary disorders	Very common	hepatic function abnormal	11	3
	Common	hyperbilirubinaemiag	5	<1
Skin and subcutaneous tissue disorders	Uncommon	acute febrile neutrophilic dermatosis (Sweet's syndrome)	<1	NA
General disorders and administration site conditions	Very common	pyrexia	48	9

[a]Worst National Cancer Institute Common Terminology Criteria for Adverse Events Grade

[b] Excluding pneumonia, urinary tract infection, sepsis, septic shock and sinusitis.

[c] The most frequently reported "other infections" in study DACO-016 were: oral herpes, oral candidiasis, pharyngitis, upper respiratory tract infection, cellulitis, bronchitis, nasopharyngitis.

[d] Including enterocolitis infectious.

[e] Including haemorrhage associated with thrombocytopaenia, including fatal cases.

[f] Including preferred terms hypersensitivity, drug hypersensitivity, anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, anaphylactoid shock.

[g] In clinical studies in AML and myelodysplastic syndrome (MDS), the reporting frequency for hyperbilirubinaemia was 11% for All Grades and 2% for Grade 3-4.

*Includes events with a fatal outcome
NA=Not applicable

Description of selected adverse drug reactions

Hematologic adverse drug reactions

The most commonly reported hematologic adverse drug reactions associated with Dacogen treatment included febrile neutropenia, thrombocytopenia, neutropenia, anemia and leukopenia.

Serious bleeding-related adverse drug reactions, some of which lead to a fatal outcome, such as central nervous system (CNS) hemorrhage (2%) and gastrointestinal (GI) hemorrhage (2%), in the context of severe thrombocytopenia, were reported in patients receiving decitabine.

Hematological adverse drug reactions should be managed by routine monitoring of complete blood counts and early administration of supportive treatments as required. Supportive treatments include, administration of prophylactic antibiotics and/or growth factor support (e.g., G-CSF) for neutropenia and

transfusions for anemia or thrombocytopenia according to institutional guidelines. For situations where decitabine administration should be delayed, see section 4.2.

Infections and infestations adverse drug reactions

Serious infection related adverse drug reactions, with potentially fatal outcome, such as septic shock, sepsis, pneumonia, and other infections (viral, bacterial and fungal) were reported in patients receiving decitabine.

Gastrointestinal disorders

Occurrences of enterocolitis, including neutropenic colitis, cecities have been reported during treatment with decitabine. Enterocolitis may lead to septic complications and may be associated with fatal outcome.

Respiratory, thoracic and mediastinal disorders

Cases of interstitial lung disease (including pulmonary infiltrates, organizing pneumonia and pulmonary fibrosis) without signs of infectious etiology have been reported in patients receiving decitabine.

Differentiation syndrome

Cases of differentiation syndrome (also known as retinoic acid syndrome) have been reported in patients receiving decitabine. Differentiation syndrome may be fatal and symptoms and clinical findings include respiratory distress, pulmonary infiltrates, fever, rash, pulmonary oedema, peripheral oedema, rapid weight gain, pleural effusions, pericardial effusions, hypotension and renal dysfunction. Differentiation syndrome may occur with or without concomitant leucocytosis. Capillary leak syndrome and coagulopathy can also occur (see section 4.4).

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il

4.9 Overdose

There is no direct experience of human overdose and no specific antidote. However, early clinical study data in published literature at doses greater than 20 times higher than the current therapeutic doses, reported increased myelosuppression including prolonged neutropenia and thrombocytopenia. Toxicity is likely to manifest as exacerbations of adverse drug reactions, primarily myelosuppression. Treatment for overdose should be supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: Antineoplastic agents, antimetabolites, pyrimidine analogues; ATC Code: L01BC08

Mechanism of action

Decitabine (5-aza-2′-deoxycytidine) is a cytidine deoxynucleoside analogue that selectively inhibits DNA methyltransferases at low doses, resulting in gene promoter hypomethylation that can result in reactivation of

tumour suppressor genes, induction of cellular differentiation or cellular senescence followed by programmed cell death.

AML Clinical experience

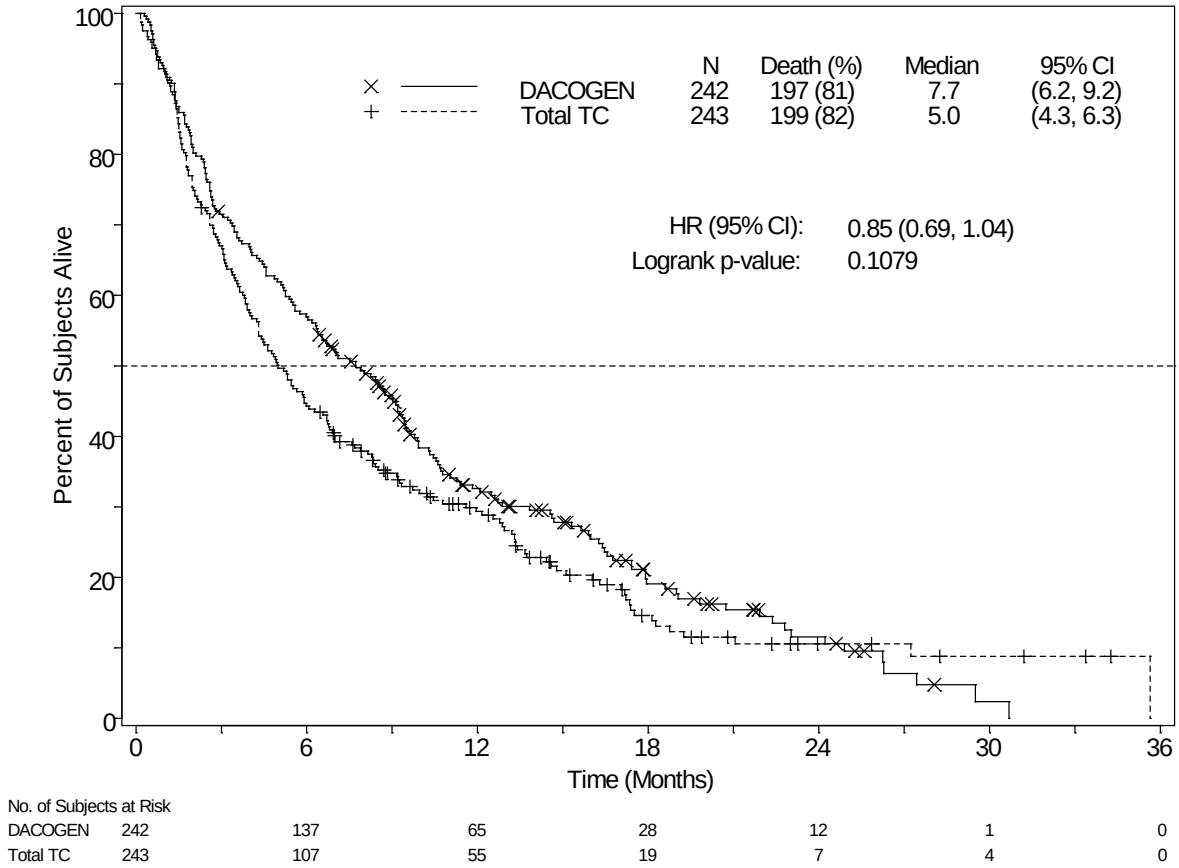
The use of Dacogen was studied in an open-label, randomised, multicentre Phase III study (DACO-016) in subjects with newly diagnosed de novo or secondary AML according to the WHO classification. Dacogen (n = 242) was compared to treatment choice (TC, n = 243) which consisted of patient's choice with physician's advice of either supportive care alone (n = 28, 11.5%) or 20 mg/m2 cytarabine subcutaneously once daily for 10 consecutive days repeated every 4 weeks (n = 215, 88.5%). Dacogen was administered as a 1-hour intravenous infusion of 20 mg/m2 once daily for 5 consecutive days repeated every 4 weeks.

Subjects who were considered candidates for standard induction chemotherapy were not included in the study as shown by the following baseline characteristics. The median age for the intent-to-treat (ITT) population was 73 years (range 64 to 91 years). Thirty-six percent of subjects had poor-risk cytogenetics at baseline. The remainder of the subjects had intermediate-risk cytogenetics. Patients with favourable cytogenetics were not included in the study. Twenty-five percent of subjects had an ECOG performance status ≥2. Eighty-one percent of subjects had significant comorbidities (e.g., infection, cardiac impairment, pulmonary impairment). The number of patients treated with Dacogen by racial group was White 209 (86.4%) and Asian 33 (13.6%).

The primary endpoint of the study was overall survival. The secondary endpoint was complete remission rate that was assessed by independent expert review. Progression-free survival and Event-free survival were tertiary endpoints.

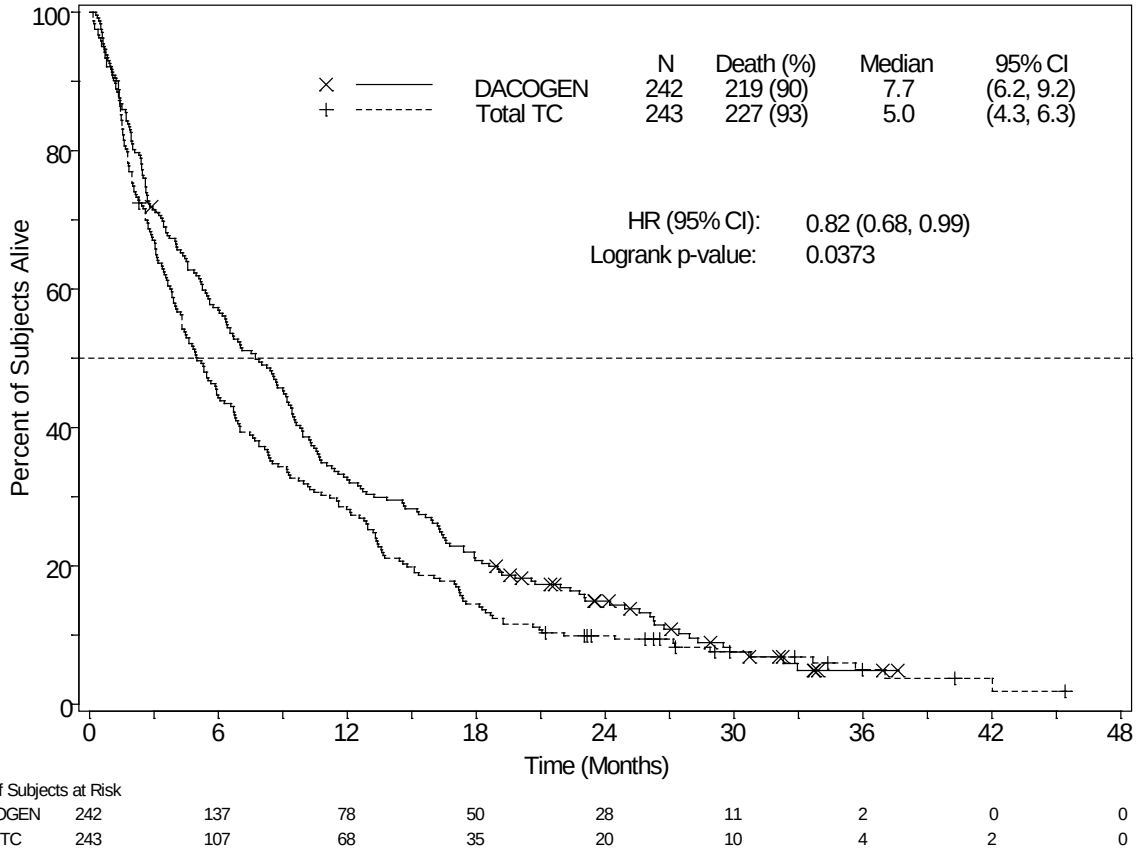
The median overall survival in the intent-to-treat ITT population was 7.7 months in subjects treated with Dacogen compared to 5.0 months for subjects in the TC arm (hazard ratio 0.85; 95% CI: 0.69, 1.04, p = 0.1079). The difference did not reach statistical significance, however, there was a trend for improvement in survival with a 15% reduction in the risk of death for subjects in the Dacogen arm (Figure 1). When censored for potentially disease modifying subsequent therapy (i.e., induction chemotherapy or hypomethylating agent) the analysis for overall survival showed a 20% reduction in the risk of death for subjects in the Dacogen arm [HR = 0.80, (95% CI: 0.64, 0.99), p-value = 0.0437)].

Figure 1. Overall Survival (Intent-to-Treat ITT Population)



In an analysis with an additional 1 year of mature survival data, the effect of Dacogen on overall survival demonstrated a clinical improvement compared to the TC arm (7.7 months vs. 5.0 months, respectively, hazard ratio = 0.82, 95% CI: 0.68, 0.99, nominal p-value = 0.0373, Figure 2)

Figure 2. Analysis of Mature Overall Survival Data (Intent-to-Treat ITT Population)



Based on the initial analysis in the Intent-to-Treat ITT population, a statistically significant difference in complete remission rate (CR + CRp) was achieved in favour of subjects in the Dacogen arm, 17.8% (43/242) compared to the TC arm, 7.8% (19/243); treatment difference 9.9% (95% CI: 4.07; 15.83),p = 0.0011. The median time to best response and median duration of best response in patients who achieved a CR or CRp were 4.3 months and 8.3 months, respectively. Progression-free survival was significantly longer for subjects in the Dacogen arm, 3.7 months (95% CI: 2.7, 4.6) compared with subjects in the TC arm, 2.1 months (95% CI: 1.9, 3.1); hazard ratio 0.75 (95% CI: 0.62, 0.91), p = 0.0031. These results as well as other endpoints are shown in Table 6.

Table 6 : Other efficacy endpoints for Study DACO-016 (ITTpopulation).

Outcomes	**DACOGEN** **n=242**	**TC (combined group)** **n= 243**	**p-value**

CR + CR_P	43 (17.8%)	19 (7.8%)	0.0011
	OR = 2.5 (1.40, 4.78)[b]		
CR	38 (15.7%)	18 (7.4%)	-
EFS[a]	3.5 (2.5, 4.1)[b]	2.1 (1.9, 2.8)[b]	0.0025
	HR = 0.75 (0.62, 0.90)[b]		
PFS[a]	3.7 (2.7, 4.6)[b]	2.1 (1.9, 3.1)[b]	0.0031
	HR = 0.75 (0.62, 0.91)[b]		

CR = complete remission; CRp = complete remission with incomplete platelet recovery, EFS = event-free survival, PFS = progression-free survival, OR = odds ratio, HR = hazard ratio

- = Not evaluable

a Reported as median months

b 95% confidence intervals

Overall survival and complete remission rates in pre-specified disease-related sub-groups (i.e., cytogenetic risk, Eastern Cooperative Oncology Group [ECOG] score, age, type of AML, and baseline bone marrow blast count) were consistent with results for the overall study population.

The use of Dacogen as initial therapy was also evaluated in an open-label, single-arm, Phase II study (DACO-017) in 55 subjects > 60 years with AML according to the WHO classification. The primary endpoint was complete remission (CR) rate that was assessed by independent expert review. The secondary endpoint of the study was overall survival. Dacogen was administered as a 1-hour intravenous infusion of 20 mg/m2 once daily for 5 consecutive days repeated every 4 weeks. In the Intent-to-Treat ITT analysis, a CR rate of 23.6% (95% CI: 13.2, 37) was observed in 13/55 subjects treated with Dacogen. The median time to CR was 4.1 months, and the median duration of CR was 18.2 months. The median overall survival in the Intent-to-Treat ITT population was 7.6 months (95% CI: 5.7, 11.5).

The efficacy and safety of Dacogen has not been evaluated in patients with acute promyelocytic leukaemia or CNS leukaemia.

MDS Clinical experience

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 7.

Table 7 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** 8:

Table 8 Response Criteria for Phase 3 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 9**) 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 9 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.

Single-arm Studies

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 inNorth America, 99 patients with IPSS Intermediate-1, Intermediate-2, or high risk prognostic scores received Dacogen 20mg/m 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 10.

Table 10 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)
S 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)
~~**Demographic or Other Patient**~~	

~~**Characteristic**~~	
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 11 Analysis of Response (ITT)*

Parameter	**Dacogen** **N=99**
Overall Response Rate (CR+PR) Complete Response (CR) Partial Response (PR)	**16 (16%)** 15 (15%) 1 (1%)
Duration of Response Median time to (CR+PR) response - Days (range) Median Duration of (CR+PR) response - Days (range)	 162 (50-267) 443 (72-722+)

+ indicates censored observation

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

5.2 Pharmacokinetic Properties

The population pharmacokinetic (PK) parameters of decitabine were pooled from 3 clinical studies in 45 patients with AML or myelodysplastic syndrome (MDS) utilizing the 5-Day regimen In each study, decitabine PK was evaluated on the fifth day of the first treatment cycle.

Distribution

The pharmacokinetics of decitabine following intravenous administration as a 1-hour infusion were described by a linear two-compartment model, characterized by rapid elimination of the drug from the central compartment and by relatively slow distribution from the peripheral compartment. For a typical patient

(weight 70 kg/body surface area 1.73 m^2) the decitabine pharmacokinetic parameters are listed in Table 12 below.

Table 12 Summary of population PK analysis for a typical patient receiving daily 1-hour infusions of Dacogen 20 mg/m^2 over 5 days every 4 weeks

Parameter[a]	Predicted Value	95% CI
C_{max} (ng/mL)	107	88.5 – 129
AUC_{cum} (ng.h/mL)	580	480 – 695
$t_{1/2}$ (min)	68.2	54.2 – 79.6
Vd_{ss} (L)	116	84.1 – 153
CL (L/h)	298	249 – 359

[a] The total dose per cycle was 100 mg/m^2

Decitabine exhibits linear PK and following the intravenous infusion, steady-state concentrations are reached within 0.5 hour. Based on model simulation, PK parameters were independent of time (i.e., did not change from cycle to cycle) and no accumulation was observed with this dosing regimen. Plasma protein binding of decitabine is negligible (<1%). Decitabine Vd_{ss} in cancer patients is large indicating distribution into peripheral tissues. There was no evidence of dependencies on age, creatinine clearance, total bilirubin, or disease.

Biotransformation

Intracellularly, decitabine is activated through sequential phosphorylation via phosphokinase activities to the corresponding triphosphate, which is then incorporated by the DNA polymerase. *In vitro* metabolism data and the human mass balance study results indicated that the cytochrome P450 system is not involved in the metabolism of decitabine. The primary route of metabolism is likely through deamination by cytidine deaminase in the liver, kidney, intestinal epithelium and blood. Results from the human mass-balance study showed that unchanged decitabine in plasma accounted for approximately 2.4% of total radioactivity in plasma. The major circulating metabolites are not believed to be pharmacologically active. The presence of these metabolites in urine together with the high total body clearance and low urinary excretion of unchanged decitabine in the urine (~4% of the dose) indicate that decitabine is appreciably metabolised *in vivo*. *In vitro* studies show that decitabine does not inhibit nor induce CYP 450 enzymes up to more than 20-fold of the therapeutic maximum observed plasma concentration (C_{max}). Thus; CYP-mediated metabolic drug interactions are not anticipated, and decitabine is unlikely to interact with agents metabolised through these pathways. In addition, in vitro data show that decitabine is a poor P-gp substrate.

Elimination

Mean plasma clearance following intravenous administration in cancer subjects was >200 L/h with moderate inter-subject variability (Coefficient of variation [CV] is approximately 50%). Excretion of unchanged drug appears to play only a minor role in the elimination of decitabine.

Results from a mass balance study with radioactive ^{14}C-decitabine in cancer patients showed that 90% of the administered dose of decitabine (4% unchanged drug) is excreted in the urine.

Additional information on special populations

The effects of renal or hepatic impairment, gender, age or race on the pharmacokinetics of decitabine have not been formally studied. Information on special populations was derived from pharmacokinetic data from the 3 studies noted above, and from one Phase I study in MDS subjects (N=14; 15 mg/m^2 x 3-hours q8h x 3 days).

Elderly

Population pharmacokinetic analysis showed that decitabine pharmacokinetics is not dependent on age (range studied 40 to 87 years; median 70 years).

Gender

Population pharmacokinetics analysis of decitabine did not show any clinically relevant difference between men and women.

Race

Most of the patients studied were Caucasian. However, the population pharmacokinetic analysis of decitabine indicated that race had no apparent effect on the exposure to decitabine.

Hepatic impairment

The PK of decitabine have not been formally studied in patients with hepatic impairment. Results from a human mass-balance study and *in vitro* experiments mentioned above indicated that the CYP enzymes are unlikely to be involved in the metabolism of decitabine. In addition, the limited data from the population PK analysis indicated no significant PK parameter dependencies on total bilirubin concentration despite a wide range of total bilirubin levels. Thus, decitabine exposure is not likely to be affected in patients with impaired hepatic function.

Renal impairment

The PK of decitabine have not been formally studied in patients with renal insufficiency. The population PK analysis on the limited decitabine data indicated no significant PK parameter dependencies on normalised creatinine clearance, an indicator of renal function. Thus, decitabine exposure is not likely to be affected in patients with impaired renal function.

5.3 Preclinical Safety Data

Formal carcinogenicity studies have not been performed with decitabine. Evidence from the literature indicates that decitabine has carcinogenic potential. The available data from in vitro and in vivo studies provide sufficient evidence that decitabine has genotoxic potential. Data from the literature also indicate that decitabine has adverse effects on all aspects of the reproductive cycle, including fertility, embryo-foetal development and post-natal development. Multi-cycle repeat-dose toxicity studies in rats and rabbits indicated that the primary toxicity was myelosuppression, including effects on bone marrow, which was reversible on cessation of treatment. Gastrointestinal toxicity was also observed and in males, testicular atrophy which did not reverse over the scheduled recovery periods. Decitabine administration to neonatal/juvenile rats showed a comparable general toxicity profile as in older rats. Neurobehavioural development and reproductive capacity

were unaffected when neonatal/juvenile rats were treated at dose levels inducing myelosuppression. See section 4.2 for information on paediatric use.

6. PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

- Monobasic Potassium phosphate
- Sodium hydroxide
- Hydrochloric acid (for pH adjustment)
- Water for injection

7. INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

8. SHELF LIFE

Unopened vial

The expiry date of the product is indicated on the packaging materials.

Reconstituted and diluted solution

Within 15 minutes of reconstitution, the concentrate (in 10 ml of sterile water for injection) must be further diluted with cold (2˚C to 8˚C) infusion fluids. This prepared diluted solution for intravenous infusion can be stored at 2˚C to 8˚C for up to maximum of 3 hours, followed by up to 1 hour at room temperature (20˚C to 25˚C) before administration.
From a microbiological point of view, the product should be used within the time period recommended above. It is the responsibility of the user to follow the recommended storage times and conditions and ensures that reconstitution has taken place in aseptic conditions.

9. SPECIAL PRECAUTIONS FOR STORAGE

Do not store above 25°C.
For storage conditions of the reconstituted and diluted medicinal product see Section 6.3.

9.1 NATURE AND CONTENTS OF CONTAINER

20 ml clear colourless Type I glass vial sealed with a butyl rubber stopper and an aluminium seal with plastic flip-off cap containing 50 mg decitabine.
Pack size: 1 vial.

9.2 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING

Recommendations for safe handling

Skin contact with the solution should be avoided and protective gloves must be worn. Standard procedures for dealing with cytotoxic medicinal products should be adopted.

Reconstitution procedure

The powder should be aseptically reconstituted with 10 ml of water for injections. Upon reconstitution, each ml contains approximately 5 mg of decitabine at pH 6.7 to 7.3. Within 15 minutes of reconstitution, the solution must be further diluted with cold infusion fluids (sodium chloride 9 mg/ml [0.9%] solution for injection or 5% glucose solution for injection) to a final concentration of 0.15 to 1.0 mg/ml. For the shelf-life and the precaution for storage after reconstitution, see section 6.3.

Dacogen should not be infused through the same intravenous access/line with other medicinal products.

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

Disposal

This medicinal product is for single use only. Any unused medicinal product or waste material should be disposed of in accordance with local requirements

10. MARKETING AUTHORIZATION NUMBER

License Holder: J-C Health Care Ltd.

KIBBUTZ SHEFAYIM, SHEFAYIM MALL, 6099000, Israel

Registration Number: 143-65-31633-00

Manufacturer: Janssen Pharmaceutica N.V.

Turnhoutseweg 30 B-2340 Beers Belgium

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