เอกสารกำกับยาภาษาอังกฤษสำหรับแพทย์

DACOGEN®

1. NAME OF THE MEDICINAL PRODUCT

1.1 Product name

DACOGEN®

1.2 Strength

Decitabine 50 mg

1.3 Pharmaceutical dosage form

Sterile powder for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 20 mL single dose vial contains 50 mg of decitabine.

After aseptic reconstitution with 10 mL of Sterile Water for Injection, each mL of the concentrate of solution for infusion contains 5 mg of decitabine.

3. PHARMACEUTICAL FORM

DACOGEN (decitabine) for Injection is a white to almost white sterile lyophilized powder.

For excipients, see *6.1 List of Excipients*.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DACOGEN is indicated for:

- the treatment of adult patients with myelodysplastic syndromes (MDS) including previously treated and untreated, de novo and secondary MDS of all French-American-British (FAB) subtypes and Intermediate-1, Intermediate-2, and High-Risk International Prognostic Scoring System (IPSS) groups.
- the treatment of adult patients with newly diagnosed de novo or secondary acute myeloid leukemia (AML), according to the World Health Organization (WHO) classification who are not candidates for standard induction chemotherapy.

  The efficacy of DACOGEN has not been fully demonstrated in patients under the age of 65 years.

4.2 Posology and method of administration

DACOGEN must be initiated under the supervision of physicians experienced in the use of chemotherapeutic agents. Complete blood and platelet counts should be performed regularly, as clinically indicated and prior to each treatment cycle.

Dosage

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. With either regimen, it is recommended that patients be treated for a minimum of 4 cycles; however, a response 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 hematological values (e.g., platelet count 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.

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

Treatment Regimen in Acute Myeloid Leukemia

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. The cycle should be repeated every 4 weeks depending on the patient's clinical response and observed toxicity. If a dose is missed, treatment should be resumed as soon as possible. It is possible to use this regimen in an outpatient setting.

Treatment Regimen in Myelodysplastic Syndromes

3-Day Dosing Treatment Regimen in MDS

In a treatment cycle, DACOGEN is administered for 3 consecutive days at a fixed dose of 15 mg/m^2 body surface area over a 3-hour period every 8 hours (i.e., a total of 9 doses per treatment cycle). This cycle is repeated approximately every 6 weeks depending on the patient's clinical response and observed toxicity. The total daily dose must not exceed 45 mg/m^2 and the total dose per treatment cycle must not exceed 135 mg/m^2. If a dose is missed, treatment should be resumed as soon as possible.

5-Day Dosing Treatment Regimen in MDS

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. The cycle should be repeated every 4 weeks depending on the patient's clinical response and observed toxicity. If a dose is missed, treatment should be resumed as soon as possible. It is possible to use this regimen in an outpatient setting.

Management of Myelosuppression and Associated Complications

Myelosuppression and adverse events related to myelosuppression (thrombocytopenia, anemia, 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 <1000/µL)
- Active viral, bacterial or fungal infection (i.e., requiring intravenous anti-infectives or extensive supportive care)
- Hemorrhage (gastrointestinal, genito-urinary, pulmonary with platelets <25000/µL or any central nervous system hemorrhage)

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).

Dose reduction is not recommended.

In MDS

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 <25000/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 >1000/µL and platelets >50000/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.

3-Day Dosing Regimen

- *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 <25000/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 >1000/µL and platelets >50000/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 weeks, 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 weeks, 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 drug and assessed for disease progression (by bone marrow aspirates) 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 discretion of the treating physician.

Special populations

Pediatrics

The safety and effectiveness in pediatric patients with MDS have not been studied.

Treatment of pediatric patients with AML is not recommended because DACOGEN was not shown to be effective in this patient population (see *5.1 Pharmacodynamic properties - Clinical studies in AML*).

Hepatic impairment

Studies in patients with hepatic impairment have not been conducted. The need for dosage adjustment in patients with hepatic impairment has not been evaluated. If worsening hepatic function occurs, patients should be carefully monitored (see *4.4 Special warnings and precautions for use, 5.2 Pharmacokinetic properties*).

Renal impairment

Studies in patients with renal impairment have not been conducted; however, data from clinical trials that included patients with mild-moderate impairment indicated no need for dosage adjustment. Patients with severe renal impairment were excluded from these trials (see *5.2 Pharmacokinetic properties*).

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 *6.4 Instructions for Use and Handling and Disposal*.

4.3 Contraindications

- Known hypersensitivity to decitabine or any of the excipients (see *6.1 List of Excipients*)

- Lactation (see *4.6 Pregnancy and lactation*)

4.4 Special warnings and 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. 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, the dose reduced or supportive measures instituted as recommended in *Dosage and Administration, Adverse reactions*.

Hepatic impairment

The use of DACOGEN in patients with hepatic impairment has not been established. Caution should be exercised in the administration of DACOGEN to patients with hepatic impairment or in patients who develop signs or symptoms of hepatic impairment. Patients should be monitored closely (see *4.2 Posology and method of administration, 5.2 Pharmacokinetic Properties*).

Renal impairment

The use of DACOGEN 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 *4.2 Posology and method of administration*).

Differentiation syndrome

Cases of differentiation syndrome (also known as retinoic acid syndrome) have been reported in patients receiving decitabine. Differentiation syndrome may be fatal. Treatment with high-dose IV corticosteroids and hemodynamic 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.

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.

4.5 Interaction 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 drugs are combined with DACOGEN.

Impact of co-administered drugs on decitabine

CYP450-mediated metabolic drug interactions are not anticipated as decitabine metabolism is not mediated by this system but by oxidative deamination. Displacement of decitabine from its plasma protein binding by co-administered drugs is unlikely given the negligible *in vitro* plasma protein binding (<1%) of decitabine. *In vitro* data indicated that decitabine is a poor P-glycoprotein (P-gp) substrate and is therefore not prone to interaction with P-gp inhibitors.

Impact of decitabine on co-administered drugs

Given its low *in vitro* plasma protein binding (<1%), decitabine is unlikely to displace co-administered drugs from their plasma protein binding. *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 is unlikely to interact with agents metabolized through these pathways. 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 drugs (see *5.2 Pharmacokinetic Properties*).

4.6 Pregnancy and lactation

Pregnancy

Women of childbearing potential should be advised to use effective contraceptive measures and avoid becoming pregnant while being treated with DACOGEN.

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 *5.3 Preclinical safety data*). 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, unless clearly necessary. If this drug is used during pregnancy, or if a patient becomes pregnant while receiving DACOGEN, the patient should be apprised of the potential hazard to the fetus.

The time period following treatment with DACOGEN where it is safe to become pregnant is unknown. Women of childbearing potential should continue to use effective contraceptive measures for at least 6 months following completion of treatment.

Use in Males: Men should be advised to not father a child while receiving DACOGEN, and for 3 months following completion of treatment (see *5.3 Preclinical safety data*).

Fertility

Female patients of childbearing potential should be advised to seek consultation regarding oocyte cryopreservation prior to initiation of treatment with DACOGEN. 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 treatment.

Breast-feeding

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

4.7 Effects on ability to drive and use machines

No studies of the effects on the ability to drive or use machines with DACOGEN have been performed. 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

Clinical Study Data

Throughout this section, adverse reactions are presented. Adverse reactions are adverse events that were considered to be reasonably associated with the use of DACOGEN based on the comprehensive assessment of the available adverse event information. A causal relationship with DACOGEN cannot be reliably established in individual cases. Further, 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 clinical practice.

The most important and frequently occurring adverse reactions in both the 5-Day and 3-Day regimens are myelosuppression and those occurring as a consequence of myelosuppression.

Adverse Reactions

The safety of DACOGEN was evaluated in 682 subjects from AML and MDS clinical studies (D-0007, DACO-016, DACO-017, DACO-020, EORTC-06011 and ID03-0180). In these clinical studies, DACOGEN was administered with the 5-Day or 3-Day dosing regimen. Adverse reactions reported during these clinical studies are summarized below in Table 1. The adverse reactions are listed by frequency category. Frequency categories are defined as follows: Very common (≥1/10), Common (≥1/100 to <1/10) and Uncommon (≥1/1000 to <1/100).

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

Table 1: Adverse Reactions Identified with DACOGEN

System Organ Class	Frequency (all Grades)	Adverse Reaction	Frequency	
			All Grades[a] (%)	Grades 3-4[a] (%)
Infections and infestations	Very common	pneumonia[*]	20	17
		urinary tract infection[*]	10	4
		other infections (all viral, bacterial, fungal infections including fatal)[*,b]	62	35
	Common	septic shock[*]	3	2
		sepsis[*]	8	7
		sinusitis	5	1
Blood and lymphatic disorders	Very common	febrile neutropenia[*]	29	27
		neutropenia[*]	32	30
		Thrombocytopenia[c*]	35	33
		anemia	33	20
		leucopenia	14	12
	Common	pancytopenia[*]	1	1
Immune system disorders	Common	hypersensitivity including anaphylactic reaction[d]	4	<1
Nervous system disorders	Very common	headache	20	1
Respiratory, thoracic and mediastinal disorders	Very common	epistaxis	15	2

Table 1: Adverse Reactions Identified with DACOGEN

System Organ Class	Frequency (all Grades)	Adverse Reaction	Frequency	
			All Grades[a] (%)	Grades 3-4[a] (%)
Gastrointestinal disorders	Very common	diarrhea	31	2
		vomiting	19	1
		stomatitis	10	2
		nausea	38	1
Skin and subcutaneous tissue disorders	Uncommon	acute febrile neutrophilic dermatosis (Sweet's syndrome)	<1	<1
General disorders and administration site conditions	Very common	pyrexia	40	6

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

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

[c] Including hemorrhage associated with thrombocytopenia, including fatal cases

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

* Includes events with a fatal outcome

Description of selected adverse reactions

Hematologic adverse reactions

The most commonly reported hematologic adverse reactions associated with DACOGEN treatment included febrile neutropenia, thrombocytopenia, neutropenia, anemia and leucopenia.

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 CNS hemorrhage (1%) and gastrointestinal hemorrhage (2%), in the context of severe thrombocytopenia, were reported in patients receiving DACOGEN.

Hematological adverse reactions should be managed by routine monitoring of complete blood counts and 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 anaemia or thrombocytopenia according to institutional guidelines. For situations where decitabine administration should be delayed, see *4.2 Posology and method of administration.*

Postmarketing Data

In addition to the adverse reactions reported during clinical studies and listed above, the following adverse reactions have been reported during postmarketing experience. Because these reactions were 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. In the table, the frequencies are provided according to the following convention:

Very common	≥ 1/10
Common	≥ 1/100 and < 1/10
Uncommon	≥ 1/ 1000 and < 1/100
Rare	≥ 1/10000 and < 1/1000
Very rare	< 1/10000, including isolated reports
Not known	Cannot be estimated from the available data

Table 2: Adverse Reactions Identified During Postmarketing Experience with DACOGEN	
System Organ Class Adverse Reaction	**Frequency Category Estimated from Spontaneous Reporting Rates**
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	
Differentiation syndrome	Very rare
Cardiac disorders	
Cardiomyopathy (including decreased ejection fraction)	Very Rare
Hepatobiliary disorders	
Hepatic function abnormal	Very rare
Hyperbilirubinemia	Very rare
Metabolism and nutrition disorders	
Hyperglycemia	Very rare

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 reactions, primarily myelosuppression (see *4.8 Undesirable effects*). Treatment for overdose should be supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and Immunomodulating Agent, Pyrimidine Analogues.

ATC Code: L01BC08

Mechanism of action

Decitabine (5-aza-2′-deoxycytidine) is a cytosine nucleoside analogue that selectively inhibits DNA methyltransferases at low doses, resulting in gene promoter hypomethylation that can result in reactivation of tumor suppressor genes, induction of cellular differentiation or cellular senescence followed by programmed cell death.

Clinical Studies

Clinical studies in MDS

Phase 2 Study (DACO-020): 5-Day Dosing Regimen

An open-label, single arm, multicenter study (DACO-20) was conducted to evaluate the efficacy of DACOGEN in MDS patients with any of the FAB subtypes. In this study, 99 patients with IPSS Intermediate-1, Intermediate-2, or high risk prognostic scores received DACOGEN by the 5-Day dosing regimen of 20 mg/m^2 intravenous infusion over 1-hour daily, on Days 1 to 5 every 4 weeks (1 cycle). The results were consistent with the results of the Phase 3 study and summarized in Table 3.

Table 3: Efficacy of DACOGEN in Phase 2 Study DACO-020

Parameter	**DACOGEN (N=99)**
Overall Response Rate (CR+mCR+PR)	33 (33%)
Complete Remission (CR)	17 (17%)
Marrow Complete Remission (mCR)	16 (16%)
Overall Improvement Rate (CR+mCR+PR+HI)	51 (52%)

CR=complete remission; mCR=marrow complete remission;

PR=partial remission; HI= hematological improvement;

Source: DACO-020 CSR

Phase 3 Study (D-0007): 3-Day Dosing Regimen

A randomized, open-label multicenter, controlled study (D-0007) evaluated DACOGEN in 170 subjects with MDS meeting FAB classification criteria and IPSS High Risk, Intermediate-2, and Intermediate-1 prognostic scores. DACOGEN was administered as the 3-Day dosing regimen of 15 mg/m^2, by continuous intravenous infusion over 3 hours repeated every 8 hours for 3 consecutive days of every 6-weeks cycle.

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.

In the Phase 3 clinical study, CRs and PRs were seen across all IPSS subgroups. However, a greater beneficial effect was evident in the subgroups of patients classified as Int-2 and High Risk, see Table 4.

Table 4: Efficacy by IPSS Subgroup in Study D-0007

	DACOGEN		Supportive care	
IPSS Subgroup	**Overall Response Rate (CR + PR)**	**Median Time (days) to AML or Death**	**Overall Response Rate (CR + PR)**	**Median Time (days) to AML or Death**
All patients	15/89 (17%)	340	0/81	219
Int-2 & High Risk	11/61 (18%)	335	0/57	189
Int-2	7/38 (18%)	371	0/36	263
High Risk	4/23 (17%)	260	0/21	79

AML= acute myeloid leukemia; CR= complete remission; IPSS= International Prognostic Scoring System; Int-2= Intermediate-2; PR= partial remission

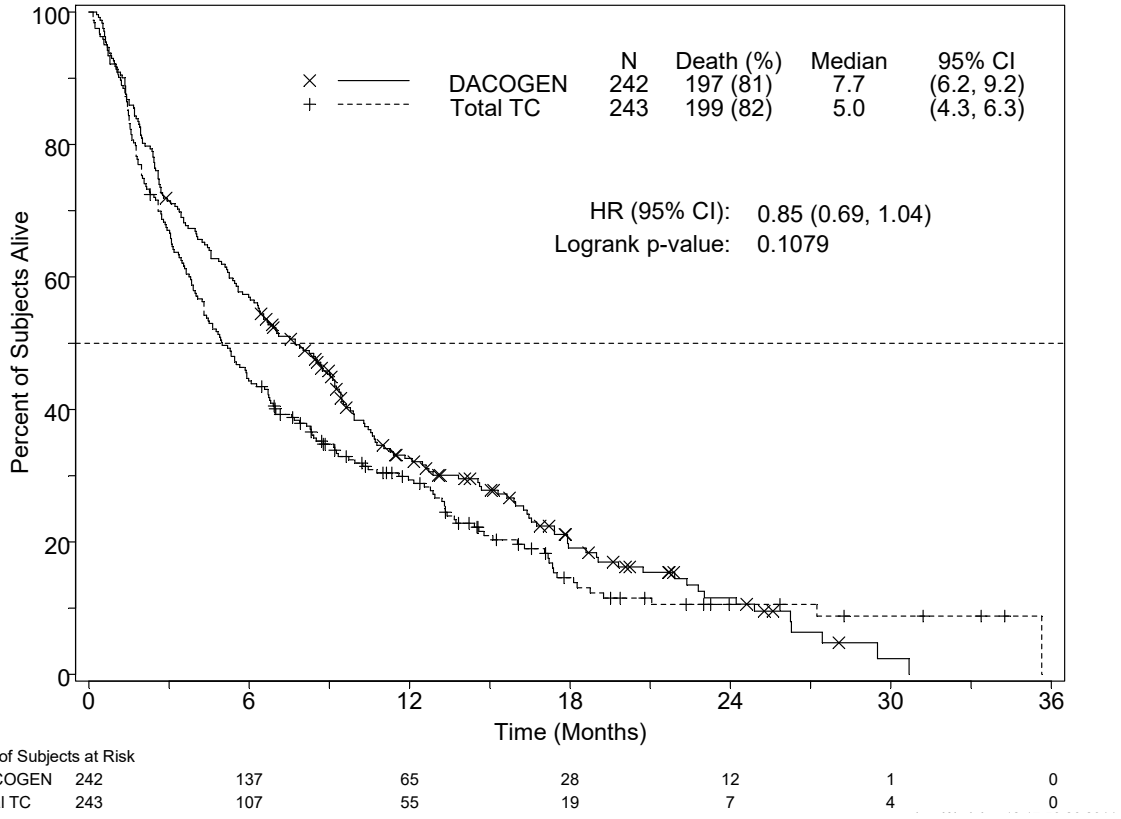
Source: D-0007 CSR

Clinical studies in AML

The use of DACOGEN was studied in an open-label, randomized, multicenter Phase 3 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/m^2 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/m^2 once daily for 5 consecutive days repeated every 4 weeks. 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. 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.

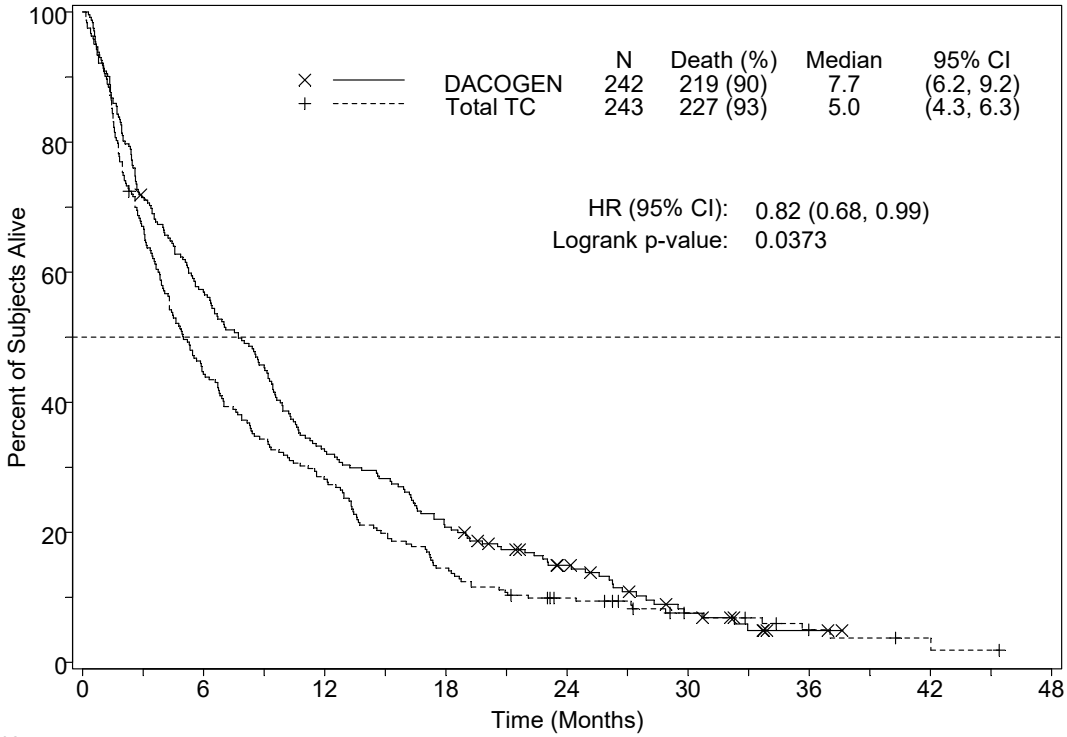
The median overall survival in the ITT population was 7.7 months in subjects treated with DACOGEN compared to 5.0 months for subjects in the TC arm (hazard ratio [HR] 0.85; 95% CI: 0.69, 1.04, p=0.1079). The difference did not reach statistical significance, however, there was a trend for improvement 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 Population)



In an analysis with an additional 1 year of mature survival data, the effect of DACOGEN on overall survival demonstrated a clinically meaningful improvement compared to the TC arm (7.7 months versus 5.0 months, respectively, HR=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 Population)



Based on the initial analysis in the intent-to-treat population, a statistically significant difference in complete remission rate (CR+CRp) was achieved in favor 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); HR=0.75; 95% CI: 0.62; 0.91, p=0.0031. These results as well as other endpoints are shown in Table 5.

Table 5: Other Efficacy Endpoints for Study DACO-016 (ITT population)

Outcomes	**DACOGEN n = 242**	**TC (combined group) n = 243**	**p-value**
CR + CRp	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 2 study (DACO-017) in 55 subjects >60 years with AML according to the WHO classification. The primary endpoint was CR rate 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/m^2 once daily for 5 consecutive days repeated every 4 weeks. In the ITT analysis, a CR rate of 23.6% (95% CI: 13.2% to 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 population was 7.6 months (95% CI: 5.7, 11.5).

<u>Pediatrics</u>

A Phase 1/2 open-label, single-arm, multicentre study evaluated the safety and efficacy of DACOGEN in sequential administration with cytarabine in pediatric subjects aged 1 month to <18 years with relapsed or refractory AML. A total of 17 subjects were enrolled and received DACOGEN 20 mg/m2 in this study, of which 9 subjects received cytarabine 1 g/m2 and 8 subjects received cytarabine administered at the maximum tolerable dose of 2 g/m2. All subjects prematurely discontinued the study treatment. The reasons for treatment discontinuation included disease progression (12 [70.6%] subjects), subjects proceeding to transplant (3 [17.6%]), investigator decision (1 [5.9%]), and "other" (1 [5.9%]). No clinically relevant anti-leukemic activity with the sequential combination was observed. Reported adverse events were consistent with the known safety profile of DACOGEN in adults.

5.2 Pharmacokinetic properties

The population pharmacokinetic (PK) parameters of decitabine were pooled from 3 clinical studies [DACO-017 (n=11), DACO-020 (n=11) and DACO-016 (n=23)] utilizing the 5-Day regimen (20 mg/m^2 × 1-hour × 5 days every 4 weeks) and 1 study, DACO-018 (n=12), utilizing the 3-Day regimen (15 mg/m^2 × 3-hours every 8 hours × 3 days every 6 weeks) in MDS or AML patients. In the 5-Day regimen, decitabine PK was evaluated on the fifth day of the first treatment cycle. Total dose per cycle was 100 mg/m^2. In the 3-Day regimen, decitabine PK was evaluated after the first dose of each dosing day of the first treatment cycle. Total dose per cycle was 135 mg/m^2.

Distribution

The pharmacokinetics of decitabine following intravenous administration as a 1-hour (5-Day regimen) or 3-hour (3-Day regimen) infusion was 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 PK parameters are listed in Table 6 below.

Table 6: Summary of Population PK Analysis for a Typical Patient (5-Day and 3-Day Regimen)

	5-Day Regimen		3-Day Regimen	
Parameter	**Predicted Value**	**95% CI**	**Predicted Value**	**95% CI**
C_{max} (ng/mL)	107	88.5 – 129	42.3	35.2 – 50.6
AUC_{cum} (ng.h/mL)	580	480 – 695	1161	972 – 1390
$t_{1/2}$ (min)	68.2	54.2 – 79.6	67.5	53.6 – 78.8
Vd_{ss} (L)	116	84.1 – 153	49.6	34.9 – 65.5
CL (L/h)	298	249 – 359	201	168 – 241

AUC= area under the plasma concentration-time curve; CL= total body clearance; C_{max}= maximum observed concentration; $t_{1/2}$= terminal elimination half life; Vd_{ss}= mean volume of distribution at steady state

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 of the drug into peripheral tissues. There was no evidence of dependencies on age, creatinine clearance, total bilirubin, or disease.

Metabolism

Intracellularly, decitabine is activated through sequential phosphorylation via phosphokinase activities to the corresponding triphosphate, which is then incorporated by the DNA polymerase. In light of *in vitro* metabolism data, 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 drug in the urine (~4% of the dose) indicate that decitabine is appreciably metabolized *in vivo*. 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.

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 4 studies noted above.

Elderly

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

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 normalized creatinine clearance, an indicator of renal function. Thus, decitabine exposure is not likely to be affected in patients with impaired renal function.

Other populations

Gender

Population PK 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 PK analysis of decitabine indicated that race had no apparent effect on the exposure to decitabine.

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-fetal 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. Neurobehavioral development and reproductive capacity were unaffected when neonatal/juvenile rats were treated at dose levels inducing myelosuppression.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Potassium dihydrogen phosphate
- Sodium hydroxide

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. DACOGEN should not be infused through the same intravenous access/line with other medicinal products.

6.3 Shelf life

See expiry date on the outer pack.

6.4 Special precautions for storage

Unopened vial: Do not store above 25°C. Excursions permitted to 15 to 30°C. For storage conditions of the reconstituted medicinal product see Section *6.4 Instructions for Use and Handling and Disposal*.

Keep out of the sight and reach of children.

Instructions for Use and Handling and Disposal

This medicinal product is for single use only. Skin contact with the solution should be avoided and protective gloves must be worn. Standard procedures for dealing with anticancer agents should be adopted. DACOGEN should be aseptically reconstituted with 10 mL of Sterile Water for Injection. Upon reconstitution, each mL contains approximately 5.0 mg of decitabine at pH 6.7 to 7.3. Immediately after reconstitution, the solution should be further diluted with 0.9% Sodium Chloride Injection or 5% Dextrose Injection to a final drug concentration of 0.15 to 1.0 mg/mL. Unless used within 15 minutes of reconstitution, the diluted solution must be prepared using cold (2°C to 8°C) infusion fluids and stored at 2°C to 8°C for up to a maximum of 4 hours until administration. Any unused product or waste material should be disposed of in accordance with local requirements.

6.5 Nature and contents of container

1 carton contains 1 vial of 50 mg decitabine.

7. MARKETING AUTHORISATION HOLDER

Janssen-Cilag Ltd.

8. MARKETING AUTHORISATION NUMBER

1C 32/52(N)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17 February 2009

10. DATE OF REVISION OF THE TEXT

CCDS v. 31 March 2021_Correct Storage Condition

Imported by

Janssen-Cilag Ltd., Bangkok, Thailand

To report Suspected Adverse Reactions, please contact us at aepqcjacth@its.jnj.com

For any product information, please contact us at medinfosea@its.jnj.com

Manufactured by

BSP Pharmaceuticals S.p.A., Latina, Italy

Warning

This medicinal product may cause serious harm. It must be used only under physician's supervision.