ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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 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 medicinal products.

Posology
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.

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

Management of myelosuppression and associated complications
Myelosuppression and adverse events related to myelosuppression (thrombocytopaenia, anaemia, neutropaenia, and febrile neutropaenia) are common in both treated and untreated patients with AML. Complications of myelosuppression include infections and bleeding. Treatment may be delayed at the discretion of the treating physician, if the patient experiences myelosuppression-associated complications, such as those described below:

- Febrile neutropaenia (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 stabilised 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.

Paediatric population
Dacogen should not be used in children with AML aged < 18 years, because efficacy was not established. Currently available data are described in sections 4.8, 5.1, and 5.2.

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

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 section 4.6)

4.4 Special warnings and precautions for use

Myelosuppression
Myelosuppression and complications of myelosuppression, including infections and bleeding that occur in patients with 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 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).

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). 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 (6.67 mg) 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 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 metabolised by enzymes implicated in the inactivation of decitabine (e.g., cytidine deaminase). Therefore, caution should be exercised if these active substances are combined with decitabine.

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

Women of childbearing potential/Contraception in men and 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).

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

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.

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 anaemia during treatment. Therefore, caution should be recommended when driving a car or operating machines.

4.8 Undesirable effects

Summary of the safety profile
The most common adverse drug reactions (≥ 35%) reported are pyrexia, anaemia and thrombocytopaenia.

The most common Grade 3/4 adverse drug reactions (≥ 20%) included pneumonia, thrombocytopaenia, neutropaenia, febrile neutropaenia 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 1. 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 1: Adverse drug reactions identified with Dacogen

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 neutropaenia*	34	32
		neutropaenia*	32	30
		thrombocytopaenia*[, e]	41	38
		anaemia	38	31
		leukopaenia	20	18
	Uncommon	pancytopaenia*	< 1	< 1
Immune system disorders	Common	hypersensitivity including anaphylactic reaction[f]	1	< 1
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 disorders	Very common	diarrhoea	31	2
		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	hyperbilirubinaemia[g]	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

Haematologic adverse drug reactions
The most commonly reported haematologic adverse drug reactions associated with Dacogen treatment included febrile neutropaenia, thrombocytopaenia, neutropaenia, anaemia and leukopaenia.

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

Haematological 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 neutropaenia and transfusions for anaemia or thrombocytopaenia 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 neutropaenic colitis, caecitis 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, organising pneumonia and pulmonary fibrosis) without signs of infectious aetiology 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).

Paediatric population
The safety assessment in paediatric patients is based on the limited safety data from a Phase I/II study to evaluate pharmacokinetics, safety and efficacy of Dacogen in paediatric patients (aged 1 to 14 years) with relapsed or refractory AML (n = 17) (see section 5.1). No new safety signal was observed in this paediatric study.

Reporting of suspected adverse reactions
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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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 dose, reported increased myelosuppression including prolonged neutropaenia and thrombocytopaenia. 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.

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/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.

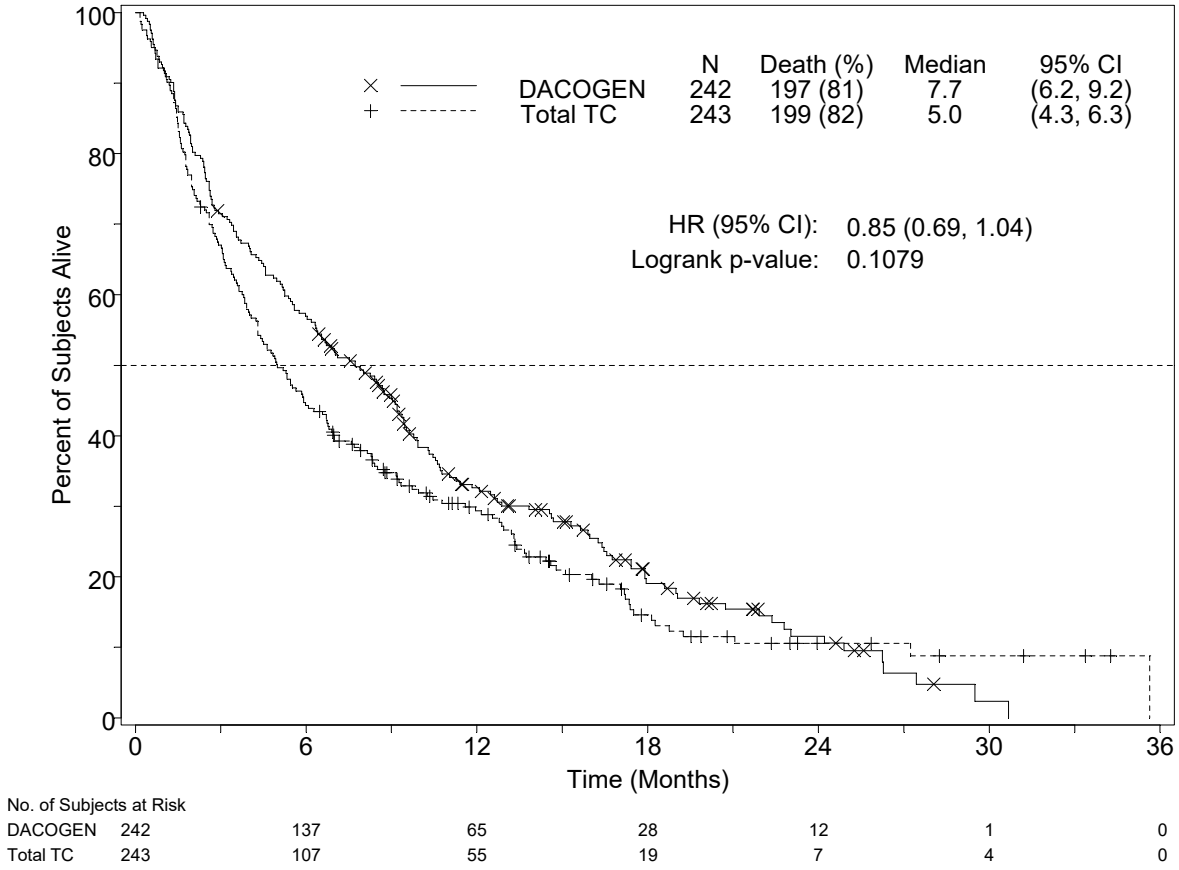
Subjects who were considered candidates for standard induction chemotherapy were not included in the study as shown by the following baseline characteristics. The median age for the intent-to-treat (ITT) population was 73 years (range 64 to 91 years). Thirty-six percent of subjects had poor-risk cytogenetics 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.

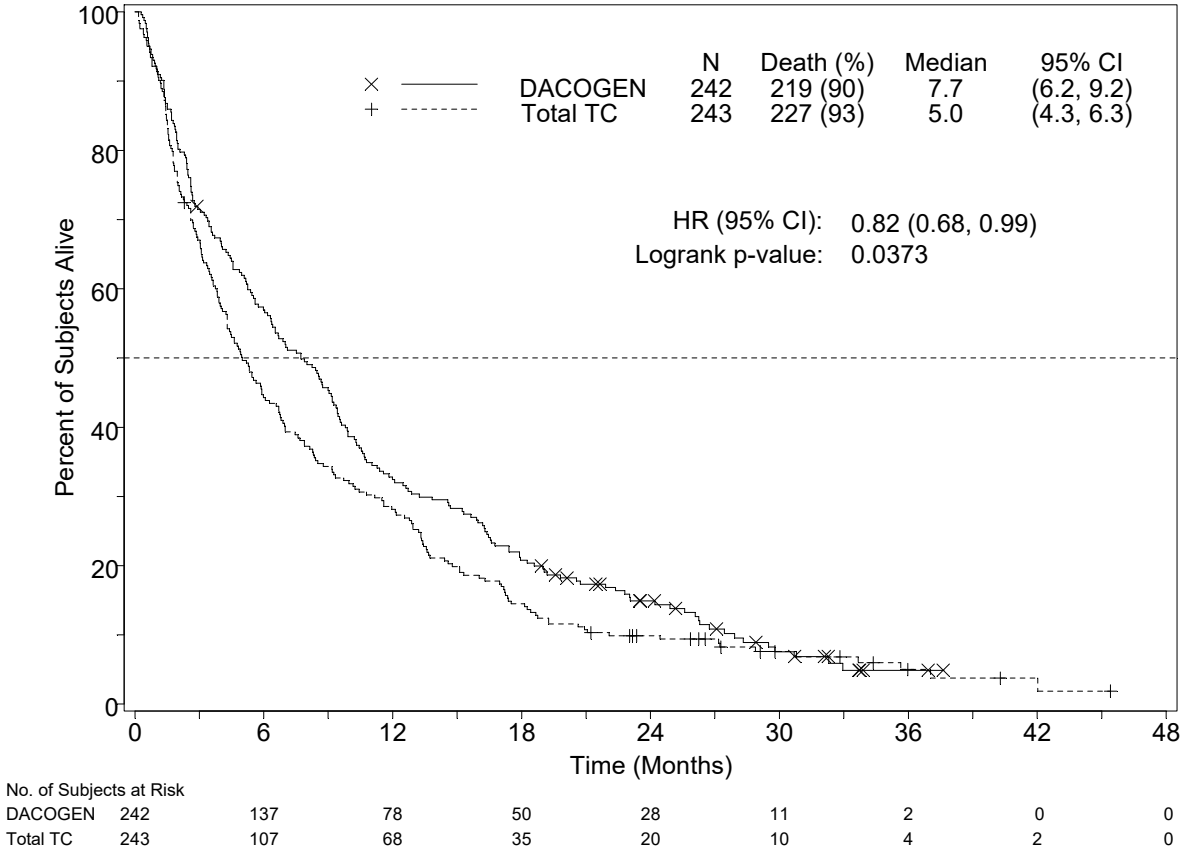
The median overall survival in the --ITT population was 7.7 months in subjects treated with Dacogen compared to 5.0 months for subjects in the TC arm (hazard ratio 0.85; 95% CI: 0.69, 1.04, p = 0.1079). The difference did not reach statistical significance, however, there was a trend for improvement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



Based on the initial analysis in the 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 2.

Table 2: 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 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/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, 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 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.

Paediatric population

A Phase I/II open-label, multicentre study evaluated the safety and efficacy of Dacogen in sequential administration with cytarabine in children aged 1 month to < 18 years with relapsed or refractory AML. A total of 17 subjects were enrolled and received Dacogen 20 mg/m^2 in this study, of which 9 subjects received cytarabine 1 g/m^2 and 8 subjects received cytarabine administered at the maximum tolerable dose of 2 g/m^2. All subjects 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%]). Reported adverse events were consistent with the known safety profile of Dacogen in adults (see section 4.8). Based on these negative results, Dacogen should not be used in children with AML aged < 18 years, because efficacy was not established (see section 4.2).

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, characterised by rapid elimination 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 the Table 3 below.

Table 3: 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 are not dependent on age (range studied 40 to 87 years; median 70 years).

Paediatric population

Population PK analysis of decitabine showed that after accounting for body size, there is no difference between decitabine PK parameters in paediatric AML patients versus adults with AML or MDS.

Gender

Population pharmacokinetic 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

Potassium dihydrogen phosphate (E340)
Sodium hydroxide (E524)
Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial
3 years.

Reconstituted and diluted solution
Within 15 minutes of reconstitution, the concentrate (in 10 ml of sterile water for injections) must be further diluted with cold (2°C - 8°C) infusion fluids. This prepared diluted solution for intravenous infusion can be stored at 2°C - 8°C for up to a maximum of 3 hours, followed by up to 1 hour at room temperature (20°C - 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 ensure that reconstitution has taken place in aseptic conditions.

6.4 Special precautions for storage

Do not store above 25°C.

For storage conditions of the reconstituted and diluted medicinal product, see section 6.3.

6.5 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.

6.6 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.

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.

7 MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

8 MARKETING AUTHORISATION NUMBER

EU/1/12/792/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 20 September 2012
Date of latest renewal: 22 May 2017

10 DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) http://www.ema.europa.eu/

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Janssen Pharmaceutica NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Dacogen 50 mg powder for concentrate for solution for infusion
decitabine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 50 mg decitabine.
After reconstitution, 1 ml concentrate contains 5 mg decitabine.

3. LIST OF EXCIPIENTS

Excipients: potassium dihydrogen phosphate (E340), sodium hydroxide (E524), and hydrochloric acid.
See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for concentrate for solution for infusion.
1 vial

5. METHOD AND ROUTE OF ADMINISTRATION

Read the package leaflet before use.
For single use only.
Intravenous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Unopened vial: Do not store above 25°C.

Read the leaflet for the shelf-life of the reconstituted and diluted product.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Janssen-Cilag International NV
Turnhoutseweg 30
B-2340 Beerse
Belgium

12. MARKETING AUTHORISATION NUMBER

EU/1/12/792/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Dacogen 50 mg powder for infusion
decitabine
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

50 mg

6. OTHER

Cytotoxic

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Dacogen 50 mg powder for concentrate for solution for infusion
decitabine

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Dacogen is and what it is used for

What Dacogen is
Dacogen is an anti-cancer medicine. It contains the active substance ‘decitabine’.

What Dacogen is used for
Dacogen is used to treat a type of cancer called ‘acute myeloid leukaemia’ or ‘AML’. This is a type of cancer that affects your blood cells. You will be given Dacogen when you are first diagnosed with AML. It is used in adults.

How Dacogen works
Dacogen works by stopping cancer cells from growing. It also kills cancer cells.

Talk to your doctor or nurse if you have any questions about how Dacogen works or why this medicine has been prescribed for you.

2. What you need to know before you are given Dacogen

Do not use Dacogen
- if you are allergic to decitabine or any of the other ingredients of this medicine (listed in section 6).
- if you are breast-feeding.

If you are not sure if any of the above applies to you, talk to your doctor, pharmacist or nurse before using Dacogen.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Dacogen if you have
- low numbers of platelets, red blood cells or white blood cells,
- an infection,
- liver disease,
- a serious kidney disorder,
- a heart disorder.

If you are not sure if any of the above applies to you, talk to your doctor, pharmacist or nurse before using Dacogen.

Dacogen can cause a serious immune reaction called 'differentiation syndrome' (see section 4 'Possible side effects').

Tests or checks
You will have blood tests before you start treatment with Dacogen and at the start of each treatment cycle. These tests are to check that:
- you have enough blood cells, and
- your liver and kidneys are working properly.

Talk to your doctor about what your blood test results mean.

Children and adolescents
Dacogen is not for use in children or adolescents under the age of 18.

Other medicines and Dacogen
Tell your doctor, nurse or pharmacist if you are using, have recently used or might use any other medicines. This includes medicines obtained without a prescription and herbal medicines. This is because Dacogen can affect the way some other medicines work. Also, some other medicines can affect the way Dacogen works.

Pregnancy and breast-feeding
- If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.
- You should not use Dacogen if you are pregnant as it may harm your baby. If you are able to become pregnant, your doctor will ask you to take a pregnancy test before you start treatment with Dacogen. Tell your doctor immediately if you become pregnant during treatment with Dacogen.
- Do not breast-feed if you are using Dacogen. This is because it is not known if the medicine passes into the mother's milk.

Male and female fertility and contraception
- Men should not father a child while using Dacogen.
- Men should use effective contraception during treatment and for up to 3 months after treatment has stopped.
- Talk to your doctor if you wish to conserve your sperm before starting treatment.
- Women who are able to become pregnant must use effective contraception during treatment and for 6 months following completion of treatment.
- Talk to your doctor if you wish to freeze your eggs before starting treatment.

Driving and using machines
You may feel tired or weak after using Dacogen. If this happens, do not drive or use any tools or machines.

Dacogen contains potassium and sodium
- This medicine contains 0.5 mmol potassium in each vial. After preparing the medicine, it contains less than 1 mmol (39 mg) of potassium per dose, i.e. essentially 'potassium- free'.
- This medicine contains 0.29 mmol (6.67 mg) sodium (main component of cooking/table salt) in each vial. After preparing the medicine, it contains between 13.8 mg-138 mg sodium per dose, equivalent to 0.7-7% of the recommended maximum daily dietary intake of sodium for an adult. Talk to your doctor if you are on a low salt diet.

3. How to use Dacogen

Dacogen will be given to you by a doctor or nurse who is trained in giving this type of medicine.

How much to use
- Your doctor will work out your dose of Dacogen. This depends on your height and weight (body surface area).
- The dose is 20 mg/m^2 body surface area.
- You will receive Dacogen every day for 5 days, then 3 weeks without the medicine. This is called a 'treatment cycle' and it is repeated every 4 weeks. You will usually receive at least 4 treatment cycles.
- Your doctor may delay your dose and change the total number of cycles, depending on how you respond to the treatment.

How Dacogen is given
The solution is given into a vein (as an infusion). This will take one hour.

If you are given more Dacogen than you should
This medicine will be given by your doctor or nurse. In the unlikely event that you are given too much (an overdose) your doctor will check you for side effects and manage them accordingly.

If you forget your appointment to have Dacogen
If you miss an appointment, make another one as soon as possible. This is because for this medicine to be as effective as possible, it is important to follow the dosing schedule.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects may happen with this medicine.

Tell your doctor or nurse immediately if you notice any of the following serious side effects
- Fever: this may be a sign of an infection caused by low levels of white blood cells (very common).
- Chest pain or shortness of breath (with or without fever or cough): these may be signs of an infection of the lung called "pneumonia" (very common) or inflamed lungs (interstitial lung disease [frequency not known]) or cardiomyopathy (heart muscle disease [uncommon]) which can be accompanied with swelling of ankles, hands, legs and feet.
- Bleeding: including blood in the stools. This may be a sign of bleeding in the stomach or gut (common).
- Difficultly with moving, speaking or understanding or seeing; sudden severe headache, seizure, numbness or weakness in any part of the body. These may be signs of bleeding inside your head (common).
- Difficulty breathing, swelling of the lips, itching or rash: This may be due to an allergic (hypersensitivity) reaction (common).
- Serious immune reaction (differentiation syndrome) that may cause fever, cough, difficulty breathing, rash, decreased urine, hypotension (low blood pressure), swelling of the arms or legs and rapid weight gain (not known).

Tell your doctor or nurse immediately if you notice any of the serious side effects above.

Other side effects of Dacogen include
Very common (may affect more than 1 in 10 people)
- urine infection

- other infection in any part of the body, caused by bacteria, virus or fungi
- bleeding or bruising more easily - these may be signs of a drop in the number of blood platelets (thrombocytopaenia)
- feeling tired or looking pale - these may be signs of a drop in the number of red blood cells (anaemia)
- high level of sugar in the blood
- headache
- nose bleeds
- diarrhoea
- vomiting
- nausea
- fever
- abnormal liver function

Common (may affect up to 1 in 10 people)
- an infection of the blood caused by bacteria - this may be a sign of a low level of white blood cells
- sore or runny nose, sore sinuses
- mouth or tongue ulcers
- high level of 'bilirubin' in the blood

Uncommon (may affect up to 1 in 100 people)
- a drop in the number of red blood cells, white blood cells and platelets (pancytopaenia)
- heart muscle disease
- red, raised painful patches on the skin, fever, an increase in white blood cells - these may be signs of 'Acute Febrile Neutrophilic Dermatosis' or 'Sweet's Syndrome'

Not known (frequency cannot be estimated from the available data)
- inflamed gut (enterocolitis, colitis and caecitis), with symptoms of abdominal pain, bloating, or diarrhoea. Enterocolitis may lead to septic complications and may be associated with fatal outcome.

Reporting of side effects
If you get side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Dacogen

- Your doctor, nurse or pharmacist is responsible for storing Dacogen.
- Keep this medicine out of the sight and reach of children.
- Do not use this medicine after the expiry date, which is stated on the carton and on the vial label after EXP. The expiry date refers to the last day of that month.
- Do not store above 25°C.
- After reconstitution, the concentrate must be further diluted within 15 minutes using cold infusion fluids. This prepared diluted solution can be stored refrigerated at 2°C - 8°C for up to a maximum of 3 hours, followed by up to 1 hour at room temperature (20°C - 25°C) before administration.
- Your doctor, nurse or pharmacist is responsible for disposing of any unused Dacogen correctly.

6. Contents of the pack and other information

What Dacogen contains

- The active substance is decitabine. Each vial of powder contains 50 mg decitabine. After reconstitution with 10 ml of water for injections, each ml of concentrate contains 5 mg of decitabine.
- The other ingredients are potassium dihydrogen phosphate (E340), sodium hydroxide(E524), and hydrochloric acid (for pH-adjustment). See section 2.

What Dacogen looks like and contents of the pack

Dacogen is a white to almost white powder for concentrate for solution for infusion. It is supplied in a 20 ml glass vial containing 50 mg decitabine. Each pack contains 1 vial.

Marketing Authorisation Holder

Janssen-Cilag International NV
Turnhoutseweg 30
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Manufacturer

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This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu/.

The following information is intended for medical or healthcare professionals only:

1. RECONSTITUTION

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.

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 (2°C - 8°C) 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 precautions for storage after reconstitution, see section 5 of the leaflet.

2. ADMINISTRATION

Infuse the reconstituted solution intravenously over 1 hour.

3. DISPOSAL

A vial is for single use only and any remaining solution must be discarded.
Any unused product or waste material should be disposed of in accordance with local requirements.