DACOGEN
decitabine
for injection

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.

For excipients, see Section List of Excipients.

PHARMACEUTICAL FORM

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

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic Properties

Pharmacotherapeutic group: Antineoplastic agent, antimetabolite pyrimidine analogue

ATC code: (To be determined)

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 tumour suppressor genes, induction of cellular differentiation or cellular senescence followed by programmed cell death. At high concentrations (> 10-4 M), decitabine is markedly cytotoxic.

In the phase III clinical study, complete (CR) and partial responses (PR) 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 3.

Table 3: Efficacy by IPSS Subgroup

IPSS Subgroup	DACOGEN		Supportive care	
	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	8/38 (21%)	371	0/36	263
High Risk	3/23 (13%)	260	0/21	79

Pharmacokinetic Properties

The pharmacokinetics of decitabine have been adequately characterized in 14 cancer patients at a dose of 15 mg/m^2 given as a 3-hour constant rate intravenous infusion every eight hours for three consecutive days.

Decitabine's pharmacokinetic profile is consistent with a multiplecompartment disposition model, with a terminal half-life of about 35 min.

There is no accumulation of decitabine in plasma when given every eight hours for three consecutive days. The pharmacokinetics reported after administration of DACOGEN daily as a 1-hour infusion for 5 consecutive days in 23 patients produced similar results.

Distribution: The steady-state volume of distribution following intravenous administration to patients with cancer is ~70 L/m^2, indicating distribution of the drug into peripheral tissues. Decitabine's (*in vitro*) plasma protein binding is negligible (<1%). In addition, decitabine is a poor P-gp substrate.

Metabolism: Intracellularly, decitabine is activated through sequential phospharylation via phosphokinase activities to the corresponding triphosphate, which is then incoporated by the DNA polymerase. *In vitro* data indicated that the cytochrome P450 system is not involved in decitabine's metabolism. Instead, the primary route of metabolism is likely through deamination by cytidine deaminase principally in the liver but also granulocytes, intestinal epithelium and plasma. To date, decitabine's *in vivo* metabolites have not been identified unequivocally. The high total body clearance and low urinary excretion of unchanged drug in the urine (<1% of the dose) suggest that decitabine is appreciably metabolized *in vivo*.

Elimination: Mean plasma clearance following intravenous administration in cancer subjects was approximately 130 L/h.m^2. Inter-subject variability was moderate (approximately 50%). Excretion of unchanged drug appears to play only a minor role in the elimination of decitabine.

Preclinical Safety Data
Carcinogenicity studies were not performed using 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 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.

CLINICAL PARTICULARS
Therapeutic Indications

DACOGEN is indicated for treatment of patients with myelodysplastic syndromes (MDS) including previously treated and untreated, de novo and secondary MDS of all French-American-British subtypes and Intermediate-1, Intermediate-2, and High-Risk International Prognostic Scoring System groups.

POSOLOGY AND METHOD OF ADMINISTRATION
DACOGEN must be administered under the supervision of physicians experienced in the treatment of MDS.

DACOGEN is administered by intravenous infusion. A central venous catheter is not required. DACOGEN must be reconstituted with 10 mL of sterile water for injection. The reconstituted solution should be further diluted for administration in an infusion of either Sodium Chloride 0.9% solution, 5% Dextrose of Lactated Ringer's solution. See Section Instructions for Use and Handling <and Disposal> for instructions in use and handling.

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

It is recommended that patients be treated for a minimum of 4 cycles; however, a complete or partial response may take longer than 4 cycles (see Dose Modification). In the phase III study, the median time to response (Complete and Partial Response) according to the International Working Group Criteria (IWG 2000), which includes transfusion independence, was three treatment cycles. Once a complete response is obtained, a minimum of 2 further cycles should be administered. There is limited clinical experience beyond 8 treatment cycles.

In a single treatment cycle, DACOGEN is administered for 3 consecutive days at a fixed dose of 15 mg/m^2 body surface area over 3-hour period every eight hours (i.e., a total of 9 doses per 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.

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

Dose Modification:
- If haemotological recovery exceeds 6 weeks, the next cycle of DACOGEN treatment should be delayed for up to 2 weeks and the dose reduced as follows:

- If recovery period is less than 8 weeks then the dose of DACOGEN for the next cycle should be reduced to 11 mg/m^2 every 8 hours for three successive days (i.e., 33 mg/m^2/day for 3 days).
- If haemotological recovery exceeds 8 weeks, the patients should be assessed for disease progression. In the absence of disease progression (i.e., with an assessment of complete remission [CR], partial remission [PR], hematologic improvement [HI] or stable disease [SD] in response to DACOGEN treatment), the dose of DACOGEN should be reduced in the next cycle to 11 mg/m^2 every eight hours (i.e., 33 mg/m^2 per day for 3 days).

- If the following biochemical abnormalities occur, the next cycle of DACOGEN therapy should be withheld until level return to within the normal range or baseline:

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

Special Populations:
Pediatric patients: The safety and effectiveness in pediatric patients have not been established.

Hepatic Impairment: The need for dosage adjustment in patients with hepatic impairment has not been evaluated (see Section Special Warnings and Special Precautions for Use).

Renal Impairment: The need for dosage adjustment in patients with renal impairment has not been evaluated (see Section Special Warnings and Special Precautions for Use).

Geriatric Patients: Geriatric patients were generally dosed at the same level as younger adults patients. Dose adjustments for toxicity should be conducted as specified for the general population.

SPECIAL WARNINGS AND SPECIAL PRECAUTIONS FOR USE
Myelosuppresion and complications of myelosuppression that occur in patients with MDS may be exacerbated with DACOGEN treatment.

Myelosuppression caused by decitabine 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 or the dose reduced as recommended in Section Posology and Method of Administration.

The use of DACOGEN in patients with renal or hepatic impairment has not been established. Caution should be exercised in the administration of DACOGEN to patients with hepatic or renal impairment and patients should be monitored closely for signs of toxicity (see Section **Pharmacokinetic Properties**)

While metabolism is extensive, the cytochrome P450 system does not appear to be involved. In clinical trials, DACOGEN was not administered to patients with serum creatinine > 2.0 mg/dL, transaminase greater than 2 times normal, or serum bilirubin > 1.5 mg/dL.

UNDESIRABLE EFFECTS

The most important and frequently occurring adverse drug reactions are myelosuppression and those occurring as a consequence of myelosuppression.

Clinical Trial Data

The safety of decitabine was evaluated in 170 subjects with myelodysplastic syndrome who participated in a Phase 3 randomized, open-label clinical trial, D0007.

Adverse Drug Reactions (ADRs) reported by ≥ 5% of DACOGEN-treated subjects in these trials are shown in Table 1.

Table 1. Adverse Drug Reactions Reported by ≥ 5% of Decitabine-treated Subjects in a Phase 3 randomized, open-label Clinical Trial of Decitabine versus Supportive Care.

MedDRA System/Organ Class Adverse Event (Preferred Term)	Decitabine (15 mg/m^2) (n=83*) %	Supportive Care (n=81) %
Infections and Infestations		
Pneumonia**	22	14
Urinary tract infection	7	2
Sinusitis	5	2
Blood and Lymphatic System Disorders		
Neutropenia**	90	72
Thrombocytopenia**	89	79
Anaemia	82	74
Febrile neutropenia	29	6
Leukopenia	28	14
Nervous System Disorders		
Headache	28	14
Respiratory, Thoracic and Mediastinal Disorders		
Epistaxis	14	19
Gastrointestinal Disorders		
Nausea	42	16
Diarrhoea	34	16
Vomiting	25	9
General Disorders and Administration Site Reactions		
Pyrexia	53	28

* Eighty-nine (89) subject were randomized to the decitabine arm; only 83 received decitabine.
** Includes events with a fatal outcome

Additional ADRs that occurred in decitabine-treated for subjects across all clinical trials for myelodysplastic syndrome and haematological and nonhaematological malignancies are listed below in Table 2.

Table 2. Adverse Drug Reactions Reported by Decitabine-treated Subjects in Clinical Trials of Decitabine for myelodysplastic syndrome, and other haematological and non-haematological malignancies

MedDRA System/Organ Class Adverse Event (Preffered Term)
Infections and Infestations
Pancytopenia** Sepsis** Septic Shock

** Includes events with a fatal outcome.

CONTRAINDICATIONS

- Known hypersensitivity to decitabine or any of the excipients (see Section List of Excipients)
- Pregnancy (see Section Pregnancy and Lactation)
- Breast feeding (see Section Pregnancy and Lactation)

INTERACTIONS WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

Impact of co-administered drugs on decitabine:

Displacement of decitabine from its plasma protein binding by coadministered drugs is unlikely given decitabine's negligible *in vitro* plasma protein binding (< 1%).

There is the potential for a pharmacokinetic drug-drug interaction with other agents, such as cytarabine, which are also activated by sequential phosphorylation (via intracellular phosphokinase activities) and/or metabolized by enzymes implicated in decitabine's inactivation (e.g., cytidine deaminase).

In vitro data indicated that decitabine is a poor P-glycoprotein (P-gp) substrate and is therefore not prone to an 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.

Decitabine is a weak inhibitor of the major human cytochrome P450 enzymes (CYP): *in vitro* IC50 values towards inhibition of CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 were in excess of 5700 ng/mL. In each case, these IC50-values are much higher than the maximum plasma concentrations of decitabine achieved in patients (plasma C_{max}-values < 100 ng/mL) treated as described in section Posology and Method of Administration.

Similarly decitabine does not induce major CYPs (CYP1A2, 2B6, 2C9, and 3A4/5) *in vitro* up to 2280 ng/mL; i.e., a concentration that substantially exceeds clinical plasma C_{max}-values at the

proposed clinical dose.

Decitabine, up to 2280 ng/mL, was also 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.

Pregnancy and Lactation

Animal data from the literature indicate that decitabine has shown reproductive toxicity in all aspects of the reproductive cycle, including fertility, embryo-foetal and post-natal development (see Section **Preclinical Safety Data**).

Use during pregnancy

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

Decitabine is teratogenic in rats and mice.

There are no adequate and well-controlled studies from the use of decitabine in pregnant women. DACOGEN is contraindicated during pregnancy. If women become pregnant while receiving DACOGEN, treatment should stop immediately, and the patient should be apprised of the potential hazard to the foetus.

Use in Males: Men should be advised to not father a child while receiving DACOGEN. Decitabine alters male fertility and is not mutagenic; therefore men treated with DACOGEN are advised not to father a child during treatments (see Section **Preclinical Safety Data**). Because of the possibility of infertility as a consequence of DACOGEN therapy, men should seek advice on conservation of sperm prior to any treatment.

Use during lactation

It is not known whether or not 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 Section Contraindications).

Effects on Ability to Drive and Use Machines

No studies have been performed on the effects of decitabine on the ability to drive or use machines. If patients experience asthenia, fatigue, dizziness, or anemia, caution should be exercised when driving or operating machinery.

Overdose

There is no direct experience of human overdose and no specific antidote.

However, early clinical trial data and published literature at doses higher than the current therapeutic ones, reported increased myelosuppression including prolonged neutropenia and thrombocytopenia. Toxicity is likely to manifest as a exacerbations of adverse drug reactions, primarily myelosuppression (see Section Undesirable Effects). Treatment for overdose should be supportive.

PHARMACEUTICAL PARTICULARS

List of Excipients

Potassium dihydrogen phosphate
Sodium hydroxide

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.

Shelf Life

Unopened vial: 3 years at 25°C. Excursions permitted to 15 to 30°C.

After reconstitution: 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 7 hours until administration.

Special Precautions for Storage

Unopened vial: Store vials at 25°C. Excursions permitted to 15 to 30°C.

For storage conditions of the reconstituted medicinal product see Section Shelf Life.

Nature and Contents of Container

Information to be supplied locally.

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 6.7-7.3.

Immediately after reconstitution, the soution should be further diluted with 0.9% Sodium Chloride Injection, 5% Dextrose Injection, or Lactated Ringer's Injection to a final drug concentration of 0.1 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 7 hours until administration.

Any unused product or waste material should be disposed of in accordance with local requirements.

HOW SUPPLIED

DACOGEN (decitabine) 50 mg/20ml
Box, 1 vial
Reg. No.:

HARUS DENGAN RESEP DOKTER

Manufactured by Pharmachemie B.V., The Netherlands
Imported and distributed by PT Johnson & Johnson Indonesia