PROFESSIONAL INFORMATION

SCHEDULING STATUS

Schedule 4

1. NAME OF THE MEDICINE

DACOGEN® powder for concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 20 mL single dose vial contains 50 mg 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.

Excipients with known effect

Each vial contains 6,67 mg sodium.

Contains less than 1 mmol sodium (23 mg) per dose and is essentially 'sodium-free'.

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.
White cake or powdery mass.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DACOGEN is indicated for the treatment of adult patients (≥ 65 years) with newly diagnosed *de novo* or secondary acute myeloid leukaemia (AML), according to the World Health Organisation (WHO) classification.

4.2 Posology and method of administration

DACOGEN must be administered under the supervision of a medical practitioner experienced in the use of chemotherapeutic agents.

Posology

Dosing regimen

A 5-Day dosing regimen in the treatment of AML is recommended. 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.

In the AML Phase 3 study, the median time to response (complete remission [CR] or CR with incomplete platelet recovery [CRp]) was 4,3 months. 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 should 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 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.

Myelosuppression and associated complications

Myelosuppression and adverse events related to myelosuppression (thrombocytopenia, anaemia, neutropenia, and febrile neutropenia) are common in both treated and untreated patients. Complications of myelosuppression include infections and bleeding. Treatment may be modified in patients experiencing myelosuppression and associated complications as described below:

Treatment may be delayed at the discretion of the treating medical practitioner, if the patient experiences myelosuppression-associated complications, such as:

- Febrile neutropenia (temperature ≥ 38,5 °C and absolute neutrophil count < 1 000/µL).

- Active viral, bacterial or fungal infection (i.e., requiring intravenous anti-infectives or extensive supportive care).
- Haemorrhage (gastrointestinal, genito-urinary, pulmonary with platelets < 25 000 / µL or any central nervous system haemorrhage).

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

Dose reduction is not recommended.

Method of administration:

DACOGEN is administered by intravenous infusion. A central venous catheter is not required.

For instructions on reconstitution and dilution of the medicine before administration, see section 6.6.

4.3 Contraindications

- DACOGEN is contraindicated in known hypersensitivity to decitabine or any of the excipients (see Section 6.1 for a list of excipients).
- DACOGEN is contraindicated in lactating women (see Section 4.6).

4.4 Special warnings and precautions for use

Myelosuppression

Myelosuppression and complications of myelosuppression, including infections and bleeding are likely to occur with DACOGEN treatment.

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 (see Section 4.2).

Haematological adverse medicine 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 DACOGEN administration should be delayed (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.

Special Populations

Paediatric patients

Treatment of paediatric patients with AML is not recommended because DACOGEN was not shown to be effective in this patient population.

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. 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 carefully monitored. (see Sections 4.8 and 5.2).

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 Section 5.2).

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 Section 4.2).

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 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 medicines and other forms of interaction

No formal clinical medicine interaction studies with decitabine have been conducted.

There is the potential for a medicine - medicine 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 medicines are combined with DACOGEN.

Impact of co-administered medicines on DACOGEN

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

Impact of DACOGEN on co-administered medicines

Given its low *in vitro* plasma protein binding (< 1 %), DACOGEN is unlikely to displace co-administered medicines from their plasma protein binding. *In vitro* studies show that DACOGEN 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 medicine interactions are not anticipated and is unlikely to interact with agents metabolised through these pathways. DACOGEN 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 medicines (see Section 5.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception in males and females

Women of childbearing potential should be advised to use effective contraceptive measures and avoid becoming pregnant while being treated with DACOGEN. 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 not to father a child while receiving DACOGEN, and for 3 months following completion of treatment (see Section 5.3).

Pregnancy

There are no adequate data on the use of DACOGEN in pregnant women. Studies have shown that DACOGEN 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.

If this medicine is used during pregnancy, or if a patient becomes pregnant while receiving DACOGEN, the patient should be apprised of the potential hazard to the foetus.

Breastfeeding

It is not known whether DACOGEN or its metabolites are excreted in breast milk. DACOGEN is contraindicated during lactation; therefore, if treatment with DACOGEN is required, breastfeeding must be

discontinued (see Section 4.3).

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 seek advice on conservation of sperm prior to any treatment.

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

4.8 Undesirable effects

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

Clinical Study Data

Throughout this section, adverse medicine reactions are reported. Adverse medicine 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.

Adverse Reactions

The safety of DACOGEN was evaluated in 682 subjects from clinical studies (D-0007, DACO-016, DACO-017, DACO-020, EORTC-06011 and ID03-0180). Adverse medicine reactions reported during these clinical studies are summarised below in Table 1. The adverse medicine reactions are listed by frequency category. Frequency categories are defined as follows: Very common (≥ 1/10), Common (≥ 1/100 to < 1/10) and Uncommon (≥ 1/1 000 to < 1/100).

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

Table 1: Adverse Medicine Reactions Identified with DACOGEN

System Organ Class	Frequency (all Grades)	Adverse Medicine 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

		anaemia	33	20
		leukopenia	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
Gastrointestinal disorders	Very common	diarrhoea	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 haemorrhage associated with thrombocytopaenia, including fatal cases.*

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

** Includes events with fatal outcome.*

Description of selected adverse medicine reactions

Haematologic adverse medicine reactions

The most commonly reported haematologic adverse medicine reactions associated with DACOGEN treatment included febrile neutropenia, thrombocytopenia, neutropenia, anaemia and leukopenia.

Serious infection-related adverse medicine reactions such as septic shock, sepsis, and pneumonia were reported in patients receiving DACOGEN.

Serious bleeding-related adverse medicine reactions such as CNS haemorrhage (1 %) and gastrointestinal haemorrhage (2 %), in the context of severe thrombocytopenia, were reported in patients receiving DACOGEN.

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.

Neoplasms benign, malignant and unspecified (incl. cysts and polyps)

- Differentiation syndrome

Hepatobiliary disorders

- Abnormal hepatic function.
- Hyperbilirubinaemia.

Cardiac disorders

- Cardiomyopathy (including decreased ejection fraction)

Metabolism and nutrition disorders

- Hyperglycaemia

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions via "**6.04 Adverse Drug Reaction Reporting Form**" found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/index/8

Alternatively, suspected adverse reactions may be reported directly to Janssen Pharmaceutica (see section 7 for contact details or visit www.janssen.com).

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 Section 4.8). Treatment for overdose should be supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification

A. 26 Cytostatic agents

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

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)] utilising the 5-Day regimen (20 mg/m^2 x 1-hour x 5 days every 4 weeks) and 1 study, DACO-018 (n=12), utilising the 3-Day regimen (15 mg/m^2 x 3-hours every 8 hours x 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, characterised by

rapid elimination of the medicine 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 2 below:

Table 2: 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	1 161	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 medicine 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 medicine in the urine (~4 % of the dose) indicate that decitabine is appreciably metabolised *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 medicine 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 medicine) is excreted in the urine.

Additional information on special populations

The effects of renal or hepatic impairment, gender or age 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 has 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 has 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

potassium dihydrogen phosphate

hydrochloric acid

sodium hydroxide

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products except for those mentioned in section 6.6. DACOGEN should not be infused through the same intravenous access/line with other medicinal products.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store unopened vials at or below 25 °C. 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.

Do not freeze the reconstituted solution.

6.5 Nature and contents of container

20 mL glass vial, stoppered with a grey bromobutyl stopper, and sealed with an aluminium crimp seal with a red plastic flip-off cap.

6.6 Special precautions for disposal and other handling

This medicinal product is for single use only.

Recommendations for safe handling

Skin contact with the solution should be avoided and protective gloves must be worn. Standard procedures for dealing with anticancer agents should be adopted.

Reconstitution procedure

DACOGEN should be aseptically reconstituted with 10 mL of Sterile Water for Injection. Upon reconstitution, each mL contains approximately 5,0 mg of DACOGEN at pH 6,7 to 7,3. Immediately after reconstitution, the solution should be further diluted with 0,9 % Sodium Chloride Injection, 5 % Dextrose Injection, to a final medicine 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 as medical waste.

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 HOLDER OF CERTIFICATE OF REGISTRATION

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