Professional information

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

DECEQ 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:

Contains potassium and sodium.

Sugar free.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White to almost white lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

DECEQ 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

DECEQ must be administered under the supervision of a medical practitioner experienced in the use of chemotherapeutic medicines.

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.

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 DECEQ 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, DECEQ 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 (CNS)).

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

Method of administration:

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

DECEQ 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 medicines should be adopted.

For instructions on reconstitution of DECEQ before administration, see section 6.6.

4.3 Contraindications

- Hypersensitivity to decitabine or to any of the excipients listed in section 6.1.
- Breastfeeding (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 DECEQ 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.

Myelosuppression caused by DECEQ 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 DECEQ may be interrupted and/or supportive measures instituted (see sections 4.2 and 4.8).

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 thrombocytopaenia according to institutional guidelines. For situations where DECEQ administration should be delayed (section 4.2).

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 DECEQ 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 4.8 and 5.2).

Renal impairment:

Use in patients with severe renal impairment has not been studied. Caution should be exercised in the administration of DECEQ 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.

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 DECEQ 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 post-marketing setting. Patients, especially those with a history of cardiac disease, should be monitored for signs and symptoms of heart failure.

DECEQ contains potassium and sodium

This medicine contains less than 1 mmol of potassium (39 mg) and sodium (23 mg) per dose, i.e it is essentially ‘potassium-free’ and ‘sodium-free’.

Paediatric patients:

The safety and effectiveness in paediatric patients have not been established.

4.5 Interaction with other medicines and other forms of interaction

No formal clinical interaction studies with decitabine have been conducted.

There is the potential for an interaction with other medicines 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 DECEQ.

Impact of co-administered medicines on DECEQ:

Cytochrome (CYP) 450-mediated metabolic interactions are not anticipated as decitabine metabolism is not mediated by this system but by oxidative deamination. Displacement of DECEQ from its plasma protein binding by co-administered medicines is unlikely given the negligible *in vitro* plasma protein binding (< 1 %) of DECEQ. *In vitro* data indicated that DECEQ is a poor P-glycoprotein (P-gp) substrate and is therefore not prone to interaction with P-gp inhibitors.

Impact of DECEQ on co-administered medicines:

Given its low *in vitro* plasma protein binding (< 1 %), DECEQ is unlikely to displace co-administered medicines from their plasma protein binding. *In vitro* studies show that DECEQ 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 medicines metabolised through these pathways. Decitabine has been shown to be a weak inhibitor of P-gp mediated transport *in vitro* and is therefore, also not expected to affect P-gp mediated transport of co-administered medicines (see section 5.2).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential/ contraception in males and females:

Women of childbearing potential must use effective contraceptive measures and avoid becoming pregnant while being treated with DECEQ. The time period following treatment with DECEQ where it is safe to become pregnant is unknown. Men should use effective contraceptive measures and be advised to not father a child while receiving DECEQ, and for 3 months following completion of treatment.

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

Pregnancy:

There are no adequate data on the use of DECEQ in pregnant women. Studies have shown that decitabine is teratogenic in rats and mice. The potential risk for humans is unknown. Based on results from animal studies and its mechanism of action, DECEQ should not be used during pregnancy and in women of childbearing potential not using effective contraception. If DECEQ is used during pregnancy, or if a patient becomes pregnant while receiving DECEQ, the patient should be apprised of the potential hazard to the foetus.

Breastfeeding:

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

No studies of the effects on the ability to drive or use machines with DECEQ 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

Summary of the safety profile

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

Infections and infestations:

Frequent: pneumonia, urinary tract infection, septic shock*, sepsis*, sinusitis, all other infections (viral, bacterial, fungal)*[, b]

Blood and the lymphatic system disorders:

Frequent: febrile neutropenia*, neutropenia, thrombocytopenia [a], anaemia, leukopenia, panctocytopenia

Immune system disorders:

Frequent: hypersensitivity including anaphylactic reaction

Metabolism and nutrition disorders:

Frequent: hyperglycaemia

Nervous system disorders:

Frequent: headache

Cardiac disorders:

Less frequent: cardiomyopathy

Respiratory, thoracic and mediastinal disorders:

Frequent: epistaxis

Gastrointestinal disorders:

Frequent: diarrhoea, vomiting, stomatitis, nausea

Hepatobiliary disorders:

Frequent: abnormal hepatic function, hyperbilirubinaemia

Skin and subcutaneous tissue disorders:

Less frequent: acute febrile neutrophilic dermatosis (Sweet's syndrome)

General disorders and administration site conditions:

Less frequent: pyrexia

Post-marketing experience:

Respiratory, thoracic and mediastinal disorders:

Interstitial lung disease.

Gastrointestinal disorders:

Enterocolitis, including neutropenic colitis, cecitis*

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

[b] Including enterocolitis infectious.

* Includes events with a fatal outcome.

Reporting of suspected adverse reactions:

Reporting suspected adverse reactions after authorisation of DECEQ is important. It allows continued monitoring of the benefit/risk balance of DECEQ. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

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 neutropenia and thrombocytopenia. Toxicity is likely to manifest as exacerbations of adverse reactions, primarily myelosuppression. Treatment for overdose should be supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 26 Cytostatic agents.

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.

Paediatric population:

Decitabine 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 Table 1 below.

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

Table 1: Summary of population PK analysis for a typical patient receiving daily 1-hour infusions of decitabine 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)	112	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 interactions are not anticipated, and decitabine is unlikely to interact with medicines 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 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.

Special populations:

The effects of renal or hepatic impairment, gender, age or race on the pharmacokinetics of decitabine have not been formally studied.

Elderly:

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

Gender:

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

Race:

Population pharmacokinetic analysis studies of decitabine indicated that race has 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 normalized creatinine clearance, an indicator of renal function. Thus, decitabine exposure is not likely to be affected in patients with impaired renal function.

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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid (for pH adjustment)

Potassium phosphate monobasic (E340)

Sodium hydroxide (E524)

6.2 Incompatibilities

DECEQ must not be mixed with other medicines except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial:

24 months.

Store at or below 25 °C.

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 4 hours until administration.

From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, DECEQ should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Keep in the outer carton until required for use.

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

6.5 Nature and contents of container

Clear, colourless, USP type I glass vial with a rubber stopper and a red aluminium flip-off seal, packed in an outer carton.

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 medicines should be adopted.

Reconstitution procedure:

The powder should be aseptically reconstituted with 10 mL of sterile water for injections. Upon reconstitution, each mL contains approximately 5 mg of decitabine at pH 6,7 to 7,3. Immediately after 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.

DECEQ should not be infused through the same intravenous access/line with other medicines.

Disposal:

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

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0157

8. REGISTRATION NUMBER

56/26/0675

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

12 December 2023

10. DATE OF REVISION OF THE TEXT