FINAL PROFESSIONAL INFORMATION FOR ELODYST

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

ELODYST 50 mg/vial, Powder for concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 20 mL vial contains 50 mg decitabine. After reconstitution with 10 mL of sterile water for injection, each mL of the concentrate of solution for infusion contains 5 mg of decitabine.

ELODYST is sugar free.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

White to almost white lyophilized cake or powder. After reconstitution it is clear colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ELODYST 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

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 **ELODYST** 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, **ELODYST** 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 (thrombocytopaenia, anaemia, neutropaenia, and febrile neutropaenia) 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 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 **ELODYST** 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

ELODYST is for single use only. **ELODYST** is administered by intravenous infusion. A central venous catheter is not required.

4.3 Contraindications

- Known hypersensitivity to decitabine or to any of the excipients of **ELODYST** (see **section 6.1**).
- **ELODYST** is contraindicated in lactating women (see **section 4.6**).

4.4 Special warnings and precautions for use

Myelosuppresion

Myelosuppression and complications of myelosuppression, including infections and bleeding are likely to occur with **ELODYST** 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 **ELODYST** 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 neutropaenia and transfusions for anaemia or thrombocytopaenia according to institutional guidelines. For situations where **ELODYST** 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 **ELODYST** in these patients has not been established.

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**).

Special populations

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 **ELODYST** 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 **ELODYST** in patients with severe renal impairment has not been studied. Caution should be exercised in the administration of **ELODYST** to patients with severe renal impairment (creatinine clearance [CrCL] < 30 mL/min) and these patients should be monitored closely (see **section 4.2**).

Paediatric population

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

4.5 Interaction with other medicine 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 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 medicines are combined with **ELODYST**.

Impact of co-administered medicines on ELODYST

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

Impact of ELODYST on co-administered medicines

Given its low *in vitro* plasma protein binding (< 1 %), **ELODYST** is unlikely to displace co-administered medicines from their plasma protein binding. *In vitro* studies show that **ELODYST** 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. **ELODYST** 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 **ELODYST**. The time period following treatment with **ELODYST** where it is safe to become pregnant is unknown.

Use in Males: Men should be advised to not father a child while receiving **ELODYST,** and for 3 months following completion of treatment

Pregnancy

There are no adequate data on the use of **ELODYST** in pregnant women. Studies have shown that **ELODYST** is teratogenic in rats and mice.

The potential risk for humans is unknown. Based on results from animal studies and its mechanism of action, **ELODYST** should not be used during pregnancy.

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

Breastfeeding

It is not known whether **ELODYST** or its metabolites are excreted in breast milk. **ELODYST** is contraindicated during lactation; therefore, if treatment with **ELODYST** 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 **ELODYST**. Because of the possibility of infertility as a consequence of **ELODYST** 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 and use machines with **ELODYST** 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

a) Summary of the safety profile

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

b) Tabulated list of adverse reactions

Infections and infestations

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

Blood and lymphatic system disorders

Frequent: Fibrile neutropaenia*, neutropaenia*, thrombocytopaenia[c]*, anaemia, leucopaenia, pancytopaenia*

Immune system disorders

Frequent: Hypersensitivity including anaphylactic reaction[d]

Metabolism and nutrition disorders

Frequency unknown: Hyperglycaemia

Nervous system disorders

Frequent: Headache

Cardiac disorders

Frequency unknown: Cardiomyopathy (including decreased ejection fraction)

Respiratory, thoracis and mediastinal disorders

Frequent: Epistaxis

Frequency unknown: interstitial lung disease

Gastrointestinal disorders

Frequent: Diarrhoea, vomiting, stomatitis, nausea

Frequency unknown: enterocolitis, including neutropaenic colitis, caecitis*

Hepato-biliary disorders

Frequency unknown: Abnormal hepatic function, hyperbilirubineamia

Skin and subcutaneous tissue disorders

Less frequent: Acute febrile neutrophilic dermatosis (Sweet's Syndrome)

General disorders and administration site conditions

Frequent: Pyrexia

[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 hypersensitivity, anaphylactic reaction, anaphylactic shock

* Included events with fatal outcome

c) Description of selected adverse reactions

Haematologic adverse medicine reactions

The most commonly reported haematologic adverse medicine reactions associated with **ELODYST** treatment included febrile neutropaenia, thrombocytopaenia, neutropaenia, anaemia and leucopaenia. Serious infection-related adverse medicine reactions such as septic shock, sepsis, and pneumonia were reported in patients receiving **ELODYST**.

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

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. Health care providers are asked to report any suspected adverse reactions via the "6.04 Adverse Drug Reactions Reporting Form", found online under SAHPRA's publications: https://www.sahpra.org.za or to the Holder of certificate of registration through the mail: pvg.cdma@heterogroups.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 neutropaenia and thrombocytopaenia. 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

Category and Class: A 26 Cytostatic Agents

Pharmacotherapeutic group: Antineoplastic agents, antimetabolites, pyrimidine analogues**, ATC code: L01BC08**.

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

Absorption

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 1 below:

Table 1: 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.

Biotransformation

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 14C-decitabine in cancer patients showed that 90 % of the administered dose of decitabine (4 % unchanged medicine) is excreted in the urine.

Characteristics in specific groups of patients

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Acetonitrile
- Hydrochloric acid
- Nitrogen gas

- Potassium dihydrogen phosphate
- Sodium hydroxide
- Water for injection

6.2 Incompatibilities

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

6.3 Shelf life

Unopened vial: 24 months.

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 to 8 °C) infusion fluids. This prepared diluted solution for intravenous infusion can be stored at 2 °C to 8 °C for up to a maximum of 4 hours, followed by up to 1 hour at room temperature before administration.

6.4 Special precautions for storage

- Store at or below 25 °C.
- For storage conditions of the reconstituted and diluted solution, see **section 6.3**.
- Do not freeze the reconstituted solution.
- Keep the vial in the outer carton until required for use.

6.5 Nature and contents of container

20 mL Type-I, round clear fiolax tubular crimp neck finish and flat bottom glass vial with 20 mm grey colored bromobutyl rubber stopper with equidistant spacers and two semi circles at the center embossed on the top and 20 mm green colour aluminium flip off seal, packed in an outer carton.

Pack size: 1 vial

6.6 Special precautions for disposal and other 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. **ELODYST** should be aseptically reconstituted with 10 mL of sterile water for injection. Upon reconstitution, each mL contains approximately 5,0 mg of **ELODYST** 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.

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

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

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

Hetero Drugs South Africa (Pty) Ltd

Waterfall Corporate Campus

Building No. 2, First floor

74 Waterfall Drive

Midrand

2066

Telephone number: 012 644 1220

8 REGISTRATION NUMBER(S)

56/26/0927

9 DATE OF FIRST AUTHORISATION

05 September 2023

10 DATE OF REVISION OF THE TEXT

N/A