Approved Professional Information for Medicines for Human Use

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

DARBECT (powder for concentrate for solution for infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

DARBECT:

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.

Sugar free.

Contains sodium: 11.60 mg.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

DARBECT:

Before reconstitution:

White to almost white lyophilized powder.

After reconstitution:

A clear colourless solution free from visible particles.

Sterile.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

DARBECT 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.

If after 4 cycles, the patient's hematological values (e.g. platelet counts or absolute neutrophil count), have not yet 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 DARBECT 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, DARBECT 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.

Management of myelosuppression and associated complications

Myelosuppression and adverse events related to myelosuppression (thrombocytopenia, 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 DARBECT 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

DARBECT 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

DARBECT is contra-indicated in patients with known hypersensitivity to decitabine or to any of the excipients, listed in section 6.1.

DARBECT is contra-indicated in lactating women (see section 4.7).

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 by treatment with DARBECT. 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 DARBECT 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 DARBECT 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).

Special populations

Hepatic impairment

Use in patients with hepatic impairment has not been established. Caution should be exercised in the administration of DARBECT 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 4.4 and 5.2).

Renal impairment

Use in patients with severe renal impairment has not been studied. Caution should be exercised in the administration of DARBECT 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 DARBECT 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 cardiac disease history, should be monitored for signs and symptoms of heart failure.

Paediatric patients

Safety and effectiveness in paediatric patients has not been established.

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 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 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

Pregnancy

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

treated with DARBECT.

There is no adequate data on the use of DARBECT in pregnant women.

The potential risk for humans is unknown. Based on results from animal studies and its mechanism of action, DARBECT should not be used during pregnancy and in women of childbearing potential not using effective contraception. If DARBECT 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.

Lactation

It is not known whether decitabine or its metabolites are excreted in breast milk. DARBECT is contraindicated during breastfeeding; therefore, if treatment with this medicine is required, breastfeeding must be discontinued (see section 4.3).

Fertility

Men should be advised to not father a child during while receiving DARBECT and for 2 months following completion of treatment.

Because of the possibility of infertility as a consequence of DARBECT 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

DARBECT 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 important and frequently occurring adverse reaction is myelosuppression and those occurring as a consequence of myelosuppression.

Tabulated list of adverse drug reactions

SYSTEM ORGAN CLASS	ADVERSE REACTION	FREQUENCY
Infections and infestations	Pneumonia, urinary tract infection, all other infections (viral, bacterial, fungal), septic shock, sepsis, sinusitis	Frequent
Blood and lymphatic disorders	Febrile neutropenia, neutropenia, thrombocytopenia, anaemia, leukopenia	Frequent
	Pancytopenia	Less frequent
Immune system disorders	Hypersensitivity including anaphylactic reaction	Frequent

Metabolism and nutrition disorders	Hyperglycaemia	Frequent
Nervous system disorders	Headache	Frequent
Cardiac disorders	Cardiomyopathy	Less Frequent
Respiratory, thoracic and mediastinal disorders	Epistaxis	Frequent
	Interstitial lung disease	Frequency unknown
Gastrointestinal disorders	Diarrhoea, nausea, vomiting, stomatitis	Frequent
	Enterocolitis, including neutropaenic colitis, caecitis	Frequency unknown
Hepatobiliary disorders	Hepatic function abnormal, hyperbilirubinaemia	Frequent
Skin and subcutaneous tissue disorders	Acute febrile neutrophilic dermatosis (Sweet's syndrome)	Less frequent
General disorders and administration site conditions	Pyrexia	Frequent

Description of selected adverse drug reactions

Hematologic adverse drug reactions

The most commonly reported hematologic adverse drug reactions associated with DARBECT treatment included febrile neutropenia, thrombocytopenia, neutropenia, anaemia and leukopenia. Serious bleeding-related adverse drug reactions, some of which lead to fatal outcome, such as central nervous system (CNS) haemorrhage (2%) and gastrointestinal (GI) haemorrhage (2%), in the context of severe thrombocytopenia, 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 neutropenia and transfusions for anaemia or thrombocytopenia 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.

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 providers are asked to report any suspected adverse reactions to SAHPRA via the

"**6.04 Adverse Medicine 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 drug reactions, primarily myelosuppression. Treatment for overdose should be supportive.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamics properties

Pharmacotherapeutic group: Antineoplastic agents, antimetabolites, pyrimidine analogues; ATC Code: L01BC08

Pharmacological classification: A. 26 Cytostatic Agents

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.

5.2 Pharmacokinetic properties

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 1 below.

Table 1: Summary of population PK analysis for a typical patient receiving daily 1-hour infusions of DARBECT 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 V_{dss} 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 metabolized 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 metabolized 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 intersubject 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.

Special populations

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).

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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The other ingredients of DARBECT are:

- Potassium dihydrogen phosphate
- Sodium Hydroxide
- Acetonitrile

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:

2 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 namely 0.9% Sodium Chloride Injection or 5% Dextrose Injection. This prepared diluted solution for intravenous infusion can be stored at 2°C - 8°C for up to a maximum of 4 hours.

6.4 Special precautions for storage

Store at or below 25 °C. Do not freeze. Protect from moisture.

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

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

DARBECT:

26 mL clear glass vial stoppered with gray igloo Lyo rubber stopper and sealed with aluminium seal having sky blue colour PP disc.

Pack size: 1 vial.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

Recommendations for safe handling

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

Reconstitution procedure:

DARBECT is administered through intravenous route. For Intravenous administration, each vial of DARBECT is to be reconstituted with 10 mL of sterile water for injection. The resulting solution will contain Decitabine in a concentration of 5 mg/mL. The reconstituted solution must be transferred to the infusion bag immediately after reconstitution.

Immediately after reconstitution, the solution should be further diluted with 0.9% Sodium Chloride Injection or 5% Dextrose Injection to a final drug concentration of 0.1 - 1.0 mg/mL. Unless used within 15 minutes of reconstitution, the diluted solution must be prepared using cold (2˚C - 8˚C) infusion fluids and stored at 2˚C - 8˚C for up to a maximum of 4 hours until administration.

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 THE CERTIFICATE OF REGISTRATION

AUROGEN SA (Pty) Ltd

Woodhill Office Park, Building 1, First Floor

53 Phillip Engelbrecht Avenue

Meyersdal, Ext. 12, 1448

Johannesburg

South Africa

8 REGISTRATION NUMBER(S)

55/26/0173.171

9 DATE OF FIRST AUTHORISATION

25 April 2023

10 DATE OF REVISION OF TEXT

N/A