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CLINICAL APPROVAL LETTER: POST REGISTRATION APPLICATIONS

Clinical approval date	28 March 2025
Applicant's cover letter date	08 July 2024
Applicant	Dr Reddys Laboratories (Pty) Ltd
Final recommendation date	13 June 2024
Proprietary name(s) (including duplicates)	Azacitidine DRL
API(s)	Azacitidine
Registration number(s)	510144
Sequence no	0014

Dear Sir/Madam,

Kindly be informed that the Authority has completed the evaluation of the above-mentioned Professional Information (PI) and Patient Information Leaflet (PIL) variation application.

1. The amendments to the PI and the PIL are approved.
2. The PI and PIL be accepted as the currently approved PI and PIL
3. The date of revision reflected on the PI and the PIL should be**: 28/03/2025**
4. The final, dated version of the above PI and PIL must be submitted to SAHPRA via email to pipilrepository@sahpra.org.za within 5 working days. For OTC products, the approved PI and PIL be uploaded onto the SAHPRA OTC Directory within 5 working days.

   Note to applicant: Amendments to any quality aspects of the medicine within the PI/PIL are subject to P&A unit approval and may only be implemented in the PI if approved by the P&A unit.

Yours Faithfully

L.DHLAMINI

MANAGER: CLINICAL POST-REGISTRATION UNIT

DR. REDDY'S LABORATORIES (PTY) LTD
PROPOSED CLEAN PROFESSIONAL INFORMATION:
AZACITIDINE DRL
(lyophilised powder for injection)
Seq 0014

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

AZACITIDINE DRL lyophilised powder for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg azacitidine.

The reconstituted suspension contains 25 mg/ml azacitidine.

Excipient with known effect:

100 mg mannitol per vial

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

White to off - white lyophilised powder for injection.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AZACITIDINE DRL is indicated for the treatment of adult patients with myelodysplastic syndromes (MDS) including the following subtypes of the French-American-British classification:

- Refractory anaemia (RA) according to the French-American-British classification (FAB) system, plus neutropenia or thrombocytopenia or requiring transfusions;
- Refractory anaemia with ringed sideroblasts (RARS) according to the FAB system, plus neutropenia or thrombocytopenia or requiring transfusions;
- Refractory anaemia with excess blasts (RAEB) according to the FAB system;
- Refractory anaemia with excess blasts in transformation (RAEB-T) according to the FAB system (or acute myeloid leukaemia with 20 to 30 % bone marrow blasts and multilineage dysplasia according to World Health Organisation (WHO) classification).
- AZACITIDINE DRL is also indicated for treating adult patients with chronic myelomonocytic leukaemia (CMML) according to the FAB system.
- Acute myeloid leukaemia (AML) with > 30 % bone marrow blasts according to the WHO classification, in patients who are not eligible for hematopoietic stem cell transplantation (HSCT).

4.2 Posology and Method of Administration

Posology

The recommended starting dose for the first treatment cycle, for all patients regardless of baseline haematology laboratory values, is 75 mg/m^2 subcutaneously or intravenously, daily for seven (7) days, followed by a rest period of 21 days (28-day treatment cycle). It is recommended that patients be treated for a minimum of 6 cycles. Treatment should be continued as long as the patient continues to benefit or until disease progression.

Patients should be monitored for haematologic response/toxicity and renal toxicities (see Section 4.8), a delay in starting the next cycle or a dose reduction as described below may be necessary.

Dosage Adjustment due to haematological toxicity:

Patients with baseline blood counts (i.e., White Blood Cells (WBC) > 3,0 x 10^9/l and absolute neutrophil count (ANC) > 1,5 x10^9/l, and platelets > 75,0 x 10^9/l).

If haematological toxicity is observed following AZACITIDINE DRL treatment, the next cycle of AZACITIDINE DRL therapy should be delayed until the platelet count and the ANC have recovered. If recovery is achieved within 14 days, no dose adjustment is necessary. However, if recovery has not been achieved within 14 days, the dose should be reduced according to the following table. Following dose modifications, the cycle duration should return to 28 days.

Nadir Counts		**% Dose in the next cycle, if recovery* is not achieved within 14 days**
ANC (10^9/L)	Platelets (10^9/L	
< 1,0	< 50,0	50 %
> 1,0	> 50,0	100 %

*Recovery= counts≥ Nadir count + (0,5 x [baseline count- Nadir count])

Patients baseline blood counts (i.e., WBC < 3,0 x 10^9/l or ANC < 1,5 x 10^9/l or platelets < 75,0 x10^9/l):

Following AZACITIDINE DRL treatment, if the decrease in WBC or ANC or platelets from baseline is less than 50 %, or greater than 50 % but with an improvement in any cell line differentiation, the next cycle should not be delayed and no dose adjustment be made.

If the decrease in WBC or ANC or platelets is greater than 50 % from that prior to treatment, with no improvement in cell line differentiation, the next cycle of AZACITIDINE DRL therapy should be delayed until the platelet count and the ANC have recovered.

If recovery is achieved within 14 days, no dose adjustment is necessary. However, if recovery has not been achieved within 14 days, bone marrow cellularity should be determined. If the bone marrow cellularity is > 50 %, no dose adjustments should be made.

If bone marrow cellularity is ≤ 50 %, treatment should be delayed, and the dose reduced according to the following table:

Bone Marrow Biopsy Cellularity	**% Dose in the next cycle, if recovery is not achieved within 14 days**	
	Recovery * ≤ 21 days	**Recovery * > 21 days**
15 to 50 %	100 %	50 %
< 15 %	100 %	33 %

*Recovery= counts≥ Nadir count + (0,5 x [baseline count- Nadir count])

Following dose modifications, the cycle duration should return to 28 days.

Special Populations:

Patients with Renal Impairment:

AZACITIDINE DRL can be administered to patients with renal impairment without initial dose adjustment. If unexplained reductions in serum bicarbonate levels to less than 20 mmol/l occur, the dose should be reduced by 50 % on the next cycle. If unexplained elevations in serum creatinine or blood urea occur, the next cycle should be delayed until values return to normal or baseline and the dose should be reduced by 50 % on the next treatment cycle (see Section 4.4).

Patients with Hepatic Impairment:

No formal studies have been conducted in patients with hepatic impairment (see Section 4.4). AZACITIDINE DRL is contraindicated in patients with malignant hepatic tumours (see Sections 4.3 and 4.4).

Elderly:

No specific dose adjustments are recommended for the elderly. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function.

Paediatric population:

AZACITIDINE DRL is not recommended for use in children below 18 years of age, due to insufficient data on safety and efficacy.

Laboratory tests

Liver function tests and serum creatinine should be determined prior to initiation of therapy.
Complete blood counts should be performed prior to initiation of therapy and as needed to monitor response and toxicity, but at a minimum, prior to each treatment cycle.

Method of Administration:

AZACITIDINE DRL should be administered under the supervision of a medical practitioner qualified in the use of anticancer agents.
Patients should be premedicated with anti-emetics for nausea and vomiting.

Subcutaneous administration

- Reconstituted AZACITIDINE DRL should be injected subcutaneously into the upper arm, thigh or abdomen.
- Rotate sites for injection.
- New injections should be given at least 2,5 cm from an old site and never into areas where the site is tender, bruised, red or hard.

Intravenous administration

- AZACITIDINE DRL solution is administered intravenously.
- Administer the total dose over a period of 10 to 40 minutes.
- The administration must be completed within 1 hour of reconstitution of the AZACITIDINE DRL vial.

For instructions on reconstitution of the medicine, see Section 6.6.

4.3 Contraindications

AZACITIDINE DRL is contraindicated in the following:

- Patients who have a known hypersensitivity to azacitidine or to any of its excipients (see Section 6.1).
- Patients with advanced malignant hepatic tumours (see Section 4.4).
- Patients must not receive live vaccines while being treated with AZACITIDINE DRL.
- Pregnancy and breastfeeding (see Section 4.6).
- AZACITIDINE DRL is not recommended for use in children and adolescents below the age of 18.

4.4 Special warnings and precautions for use

Haematological toxicity

Treatment with AZACITIDINE DRL is associated with anaemia, neutropenia and thrombocytopenia, particularly during the first 2 cycles (see Section 4.8).
At least prior to each treatment cycle, complete blood counts should be performed as needed to monitor response and toxicity. After administration of the recommended dose for the first cycle, the dose for subsequent cycles should be reduced or its administration delayed based on nadir counts and haematological response (see Section 4.2). Patients should be advised to promptly report febrile episodes. Patients and physicians should be advised to be observant for signs and symptoms of bleeding.

Hepatic impairment

No formal studies have been conducted in patients with hepatic impairment. Patients suffering with extensive tumour burden due to metastatic disease and especially such patients with baseline serum albumin < 30 g/l have experienced progressive hepatic coma and death during AZACITIDINE DRL treatment. AZACITIDINE DRL is contraindicated in patients with advanced malignant hepatic tumours (see Section 4.3).

Renal impairment

Renal abnormalities ranging from elevated serum creatinine to renal failure and death were reported in patients treated with intravenous (IV) AZACITIDINE DRL in combination with other chemotherapeutic agents for non-MDS conditions. In addition, renal tubular acidosis, (defined as a fall in serum bicarbonate to < 20 mmol/l in association with an alkaline urine and hypokalaemia (serum potassium < 3 mmol/l) developed in [~~5~~] subject with chronic myelogenous leukaemia (CML) who were treated with azacitidine and etoposide. If unexplained reductions in serum bicarbonate (< 20 mmol/l) or elevations of serum creatinine or BUN (blood urea nitrogen) occur, the dose should be reduced or administration delayed.

Patients should be advised to report oliguria and anuria to their healthcare professional immediately.

Patients with renal impairment should be closely monitored for toxicity since azacitidine and/or its metabolites are primarily excreted by the kidney (see Section 4.2).

Laboratory tests

Liver function tests, serum creatinine and serum bicarbonate should be determined prior to initiation of therapy and prior to each treatment cycle. Complete blood counts should be performed prior to initiation of therapy and as needed to monitor response and toxicity, but at a minimum, prior to each treatment cycle (see Sections 4.2 and 4,8).

Cardiac and pulmonary disease

Safety and efficacy of AZACITIDINE DRL has not been established in patients with a history of severe congestive heart failure, clinically unstable cardiac disease or pulmonary disease. It is therefore advised to exercise caution when prescribing AZACITIDINE DRL to these patients. A cardiopulmonary assessment before and during the treatment should be considered.

Necrotising fasciitis

Necrotising fasciitis, including fatal cases, have been reported in patients treated with azacitidine. Treatment with AZACITIDINE DRL should be discontinued in patients who develop necrotising fasciitis and appropriate treatment should be promptly initiated.

Tumour lysis syndrome

The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

Differentiation syndrome

Cases of differentiation syndrome (also known as retinoic acid syndrome) have been reported in patients receiving injectable azacitidine as contained in AZACITIDINE DRL. Differentiation syndrome may be fatal and symptoms and clinical findings include respiratory distress, pulmonary infiltrates, fever, rash, pulmonary oedema, peripheral oedema, rapid weight gain, pleural effusions, pericardial effusions, hypotension and renal dysfunction (see Section 4.8).
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 injectable azacitidine should be considered until resolution of symptoms and if resumed, caution is advised.

AZACITIDINE DRL contains mannitol and may have a laxative effect.

4.5 Interaction with other medicines and other forms of interaction

No formal clinical drug interaction studies have been conducted with AZACITIDINE DRL. Based on *in vitro* data, azacitidine metabolism does not appear to be mediated by cytochrome P450 isoenzymes (CYPs), UDP- glucuronosyltransferases (UGTs), sulfotransferases (SULTs), and glutathione transferases (GSTs). Therefore, interactions related to these metabolising enzymes, *in vivo,* are considered unlikely.

Clinically significant inhibitory or inductive effects of azacitidine on cytochrome P450 enzymes are unlikely (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 avoid falling pregnant while taking AZACITIDINE DRL.
Women of childbearing potential must use highly effective contraception during and for at least 6 months after treatment.
Men should be advised not to father a child while receiving treatment and must use effective contraception during and for at least 3 months after treatment.

Pregnancy

AZACITIDINE DRL may cause foetal harm when administered to a pregnant woman.
Azacitidine was teratogenic in animals. If this medicine is used during pregnancy or if a patient becomes pregnant while taking AZACITIDINE DRL, the patient should be apprised of the potential hazard to the foetus.

Female partners of male patients receiving AZACITIDINE DRL should not become pregnant.

Lactation

Due to the potential serious adverse reactions in the nursing child, breast-feeding is contraindicated during AZACITIDINE DRL therapy.

Fertility

There are no human data on the effect of azacitidine on fertility. In animals, adverse reactions with azacitidine use on male fertility have been documented. Before starting treatment, male patients should be advised to seek counselling on sperm storage.

4.7 Effects on ability to drive and use machines

AZACITIDINE DRL may have minor or moderate effect on mental and/or physical abilities to perform or execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision.

Patients who experience dizziness should not drive or use machines when taking AZACITIDINE DRL.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions were gastrointestinal (nausea, vomiting and diarrhoea), haematological (anaemia, thrombocytopenia, leukopenia/neutropenia), and injection site reactions.

Adverse reactions associated with intravenously administered azacitidine were similar in frequency and severity compared with subcutaneously administered azacitidine.

Table 1: Tabulated summary of adverse reactions

System Organ Class	**Frequent**	**Less frequent**	**Frequency not known**
Infections and infestations	pneumonia* (including bacterial, viral and fungal), nasopharyngitis, sepsis* (including bacterial, viral and fungal), neutropenic sepsis*, respiratory tract infection (includes upper and bronchitis), urinary tract infection, cellulitis, diverticulitis, oral fungal infection, sinusitis, pharyngitis, rhinitis, herpes simplex, skin infection		Necrotizing fasciitis *
Neoplasms benign, malignant and unspecified (including cysts and polyps)			differentiation syndrome *(see Section 4.4)*
Blood and lymphatic system disorders	febrile neutropenia*, neutropenia, leukopenia, thrombocytopenia, anaemia, pancytopenia*, bone marrow failure		
Immune system disorders		hypersensitivity reactions	

Metabolism and nutrition disorders	anorexia, decreased appetite, hypokalemia, dehydration	tumour lysis syndrome	
Psychiatric disorders	Insomnia, confusional state, anxiety		
Nervous system disorders	dizziness, headache, intracranial haemorrhage*, syncope, somnolence, lethargy		
Eye disorders	eye haemorrhage, conjunctival haemorrhage		
Cardiac disorders	pericardial effusion	pericarditis	
Vascular disorders	hypotension*, hypertension, orthostatic hypotension, haematoma		
Respiratory, thoracic and mediastinal disorders	dyspnoea, epistaxis, pleural effusion, dyspnoea exertional, pharyngolaryngeal pain	interstitial lung disease	
Gastro-intestinal disorders	diarrhoea, vomiting, constipation, nausea, abdominal pain (includes upper and abdominal discomfort), gastrointestinal haemorrhage* (includes mouth haemorrhage), haemorrhoidal haemorrhage,		

	stomatitis, gingival bleeding, dyspepsia		
Hepato-biliary disorders		hepatic failure*, progressive hepatic coma	
Skin and sub-cutaneous tissue disorders	petechiae, pruritus (includes generalized), rash, ecchymosis, purpura, alopecia, urticaria, erythema, rash macular	acute febrile neutrophilic dermatosis, pyoderma gangrenosum	
Musculo-skeletal and connective tissue disorders	arthralgia, musculoskeletal pain (includes back, bone and pain in extremity), muscle spasms, myalgia		
Renal and urinary disorders	renal failure*, haematuria, elevated serum creatinine	renal tubular acidosis	
General disorders and administration site conditions	pyrexia*, fatigue, asthenia, chest pain, injection site erythema, injection site pain, injection site reaction (unspecified), bruising, haematoma, induration, rash, pruritus, inflammation, discoloration, nodule and haemorrhage (at injection site), malaise, chills, catheter site hemorrhage	injection site necrosis (at injection site)	

Investigations	weight decreased			

* = rarely fatal cases have been reported

Description of selected adverse reactions

Haematologic adverse reactions

The most frequently reported haematological adverse reactions associated with azacitidine treatment include anaemia, thrombocytopenia, neutropenia and leukopenia. There is a greater risk of these events occurring during the first 2 cycles, after which they occur with less frequency in patients with restoration of haematological function. Most haematological adverse reactions were managed by routine monitoring of complete blood counts and delaying azacitidine administration in the next cycle, prophylactic antibiotics and/or growth factor support (e.g., G-CSF) for neutropenia and transfusions for anaemia or thrombocytopenia as required.

Infections

Myelosuppression may lead to neutropenia and an increased risk of infection. Serious adverse reactions such as sepsis, including neutropenic sepsis, and pneumonia were reported in patients receiving azacitidine, some with a fatal outcome. Infections may be managed with the use of anti-infectives plus growth factor support (e.g., G-CSF) for neutropenia.

Bleeding

Bleeding may occur with patients receiving azacitidine. Serious adverse reactions such as gastrointestinal haemorrhage and intracranial haemorrhage have been reported. Patients should be monitored for signs and symptoms of bleeding, particularly those with pre-existing or treatment-related thrombocytopenia.

Hypersensitivity

Serious hypersensitivity reactions have been reported in patients receiving azacitidine. In case of an anaphylactic-like reaction, treatment with azacitidine should be immediately discontinued and appropriate symptomatic treatment initiated.

Skin and subcutaneous tissue adverse reactions

The majority of skin and subcutaneous adverse reactions were associated with the injection site. The majority of adverse reactions occurred during the first 2 cycles and tended to decrease with subsequent cycles. Subcutaneous adverse reactions such as injection site rash, inflammation, pruritus, erythema and skin lesion may require management with concomitant medicinal products, such as antihistamines, corticosteroids and non-steroidal anti-inflammatory medicinal products (NSAIDs).

Gastrointestinal adverse reactions

The most frequently reported gastrointestinal adverse reactions associated with azacitidine treatment included constipation, diarrhoea, nausea and vomiting. These adverse reactions were managed symptomatically with anti-emetics for nausea and vomiting; anti-diarrhoeals for diarrhoea, and laxatives and/or stool softeners for constipation.

Renal adverse reactions

Renal abnormalities, ranging from elevated serum creatinine to renal tubular acidosis, renal failure and death were reported in patients treated with azacitidine (see Section 4.4).

Hepatic adverse reactions

Patients with extensive tumour burden due to metastatic disease have been reported to experience progressive hepatic coma and death during azacitidine treatment (see Section 4.4).

Cardiac events

Data from a clinical trial allowing enrolment of patients with known history of cardiovascular or pulmonary disease showed an increase in cardiac events in patients with newly diagnosed AML treated with azacitidine (see Section 4.4).

Elderly population

There is limited safety information available with azacitidine in patients ≥ 85 years.

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 requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

4.9 Overdose

In the event of an overdose, side effects will be exaggerated (see section 4.8). The patient should be monitored with appropriate blood counts and should receive supportive treatment, as necessary. There is no known specific antidote for AZACITIDINE DRL overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A26 Cytostatic agents

Pharmacotherapeutic group: Antineoplastic agents, pyrimidine analogues; ATC code: L01BC07

Mechanism of action

Azacitidine is a cytidine nucleoside analogue that incorporates into RNA and DNA. Azacitidine is believed to exert its antineoplastic effects by cytotoxicity to abnormal haematopoietic cells in the bone marrow and hypomethylation of DNA. The cytotoxic effects of azacitidine may be due to inhibition of protein synthesis and activation of DNA damage pathways, due to incorporation into RNA and DNA, respectively. Incorporation of azacitidine into DNA also results in DNA hypomethylation and may allow the re-expression of genes involved in normal cell cycle regulation and differentiation. Non-proliferating cells are relatively insensitive to azacitidine.

5.2 Pharmacokinetic properties

The pharmacokinetics of azacitidine were studied following administrations of a single 75 mg/m^2 subcutaneous (SC) dose and a single intravenous (IV) dose.

Absorption:

Azacitidine was rapidly absorbed after the SC administration, with peak plasma concentrations of 750 ± 403 ng/ml occurring at 0,5 h after dosing.
The absolute bioavailability of azacitidine after subcutaneous relative to intravenous administration (single 75 mg/m^2 doses) was approximately 89 % based on area under the curve (AUC).
AUC and maximum plasma concentration (C_{max}) of subcutaneous administration of azacitidine were approximately proportional within the 25 to 100 mg/m^2 dose range. Multiple dosing at the recommended dose-regimen does not result in accumulation of azacitidine.

Distribution:

Following intravenous administration, the mean volume of distribution was 76 ± 26 L and systemic clearance was 167 ± 49 L/h.

Metabolism

Based on *in vitro* data, azacitidine metabolism does not appear to be mediated by cytochrome P450 isoenzymes (CYPs).

An *in vitro* study of azacitidine with cultured human hepatocytes indicates that at concentrations of 1,0 µM to 100 µM (i.e., up to approximately 30-fold higher than clinically achievable concentrations), azacitidine does not induce CYP 1A2, 2C19, or 3A4 or 3A5. In studies to assess inhibition of a series of P450 isoenzymes (CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4), azacitidine up to 100 µM did not produce inhibition. Therefore, CYP enzyme induction or inhibition by azacitidine at clinically achievable plasma concentrations is unlikely.

Excretion:

Azacitidine is cleared from plasma with a mean elimination half-life ($t_{½}$) after subcutaneous administration of 41 ± 8 minutes. Published studies indicate that urinary excretion is the primary route of elimination of azacitidine and/or its metabolites. Following intravenous and subcutaneous administration of 14C azacitidine, 85 % and 50 % of the administered radioactivity was recovered in urine respectively, while < 1 % was recovered in faeces. The mean elimination half-lives of total radioactivity (azacitidine and/or its metabolites) were similar after intravenous and subcutaneous administrations, i.e., about 4 hours.

Special Populations

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

Renal impairment:

Severe renal impairment has no major effect on the PK exposure of azacitidine after single and multiple SC administrations. Therefore, azacitidine can be administered to patients with renal impairment without initial dose adjustment.

Pharmacogenomics

The effect of known cytidine deaminase polymorphisms on azacitidine metabolism has not been formally investigated.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

Nitrogen

Water for injection

6.2 Incompatibilities

AZACITIDINE DRL must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial:

2 years

Reconstituted suspension for subcutaneous administration:

- When reconstituted with refrigerated (2 °C to 8 °C) water for injections, the reconstituted suspension can be kept in the refrigerator (2 °C to 8 °C) for a maximum of 22 hours.

- After removal from refrigerated conditions, the suspension may be allowed to equilibrate to room temperature (25 ºC) for up to 30 minutes prior to administration.

Reconstituted suspension for intravenous administration:

- When stored at 25 ºC, the reconstituted product should be administered within 1 hour.

From a microbiological point of view, the reconstituted product should be used immediately.

6.4 Special precautions for storage

Unopened vial:

Store at or below 25 °C.

Reconstituted suspension:

For storage conditions after reconstitution of the medicinal product, see Section 6.3.

6.5 Nature and contents of container

30 ml USP type I flint tubular glass vial, with a 20 mm dark grey bromobutyl rubber stopper and sealed with 20 mm violet coloured aluminium flip-off tear seal.

6.6 Special precautions for disposal and other handling

Instruction for safe handling:

- AZACITIDINE DRL is a cytotoxic medicine and, as with other potentially toxic compounds, caution should be exercised when handling and preparing AZACITIDINE DRL suspensions.
- Procedures for proper handling and disposal of anticancer medicines should be applied.
- If reconstituted AZACITIDINE DRL comes into contact with the skin, immediately and thoroughly wash with soap and water.
- If it comes into contact with mucous membranes, flush thoroughly with water.

Preparation for the subcutaneous administration:

- AZACITIDINE DRL must be reconstituted to form a uniform suspension prior to administration.
- AZACITIDINE DRL should be reconstituted aseptically with 4 ml of water for injection.
- Vigorously shake the vial until a uniform cloudy suspension is achieved.
- After reconstitution each ml of suspension will contain 25 mg of azacitidine (100 mg/4 ml).
- To provide a homogeneous suspension, the contents of the syringe must be re-suspended immediately prior to administration.
- To re-suspend, vigorously roll the syringe between the palms until a uniform cloudy suspension is achieved.
- Doses greater than 4 ml should be divided equally into two syringes and injected into two separate sites.

Preparation for the intravenous administration:

- Parenteral drug product should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
- Do not use the product if there is evidence of particulate matter or discoloration.
- Reconstitute the appropriate number of AZACITIDINE DRL vials to achieve the desired dose.
- Reconstitute each vial with 10 ml sterile water for injection.
- Vigorously shake or roll the vial until all solids are dissolved. The resulting solution will contain azacitidine 10 mg/ml.
- The solution should be clear.

- Withdraw the required amount of AZACITIDINE DRL solution to deliver the desired dose and inject into a 50 to 100 ml infusion bag of either 0,9 % sodium chloride injection or lactated ringer's injection.

- AZACITIDINE DRL is incompatible with 5 % dextrose injection solutions, Hespan or solutions that contain bicarbonate.

  These solutions have the potential to increase the rate of degradation of AZACITIDINE DRL and should therefore be avoided.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Dr. Reddy's Laboratories (Pty) Ltd.

Block B, 204 Rivonia Road

Morningside

Sandton

2057

8. REGISTRATION NUMBER

51/26/0144

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 15 September 2020

10. DATE OF REVISION OF TEXT

TBA

DR. REDDY'S LABORATORIES (PTY) LTD.
PROPOSED CLEAN PATIENT INFORMATION LEAFLET:
AZACITIDINE DRL
(lyophilised powder for injection)
Seq 0014

SCHEDULING STATUS

S4

AZACITIDINE DRL

(lyophilised powder for injection)

azacitidine

Contains sugar (mannitol)

Read all of this leaflet carefully before you are given AZACITIDINE DRL

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- AZACITIDINE DRL has been prescribed for you personally and you should not share your medicine with other people. It may harm them, even if their symptoms are the same as yours. The injection will be given to you by your medical doctor or by a qualified healthcare professional under her/his supervision.

What is in this leaflet

1. WHAT AZACITIDINE DRL is and what it is used for

AZACITIDINE DRL contains a medicine called azacitidine.

AZACITIDINE DRL is an anti-cancer medicine which belongs to a group of medicines called 'anti-metabolites'. AZACITIDINE DRL prevents cancer cells from growing.

AZACITIDINE DRL is used in adults who are not able to have a stem cell transplantation to treat:

- higher-risk myelodysplastic syndromes (MDS), a group of bone marrow disorders in which the bone marrow does not produce enough healthy blood cells;
- chronic myelomonocytic leukaemia (CMML) a type of cancer of the blood-forming cells of the bone marrow;
- acute myeloid leukaemia (AML), a cancer of the blood cells, characterised by the rapid growth of abnormal white blood cells that accumulate in the bone marrow and interfere with the production of normal blood cells.

2. What you need to know before you are given AZACITIDINE DRL

You should not be administered with AZACITIDINE DRL if:

- you are hypersensitive (allergic) to azacitidine or any of the other ingredients of AZACITIDINE DRL (see What AZACITIDINE DRL contains).
- you have liver cancer.
- Do not receive live vaccines while being treated with AZACITIDINE DRL.
- you are pregnant and/or breastfeeding.

- AZACITIDINE DRL is not recommended for use in children and adolescents below the age of 18.

Warnings and precautions

Special care should be taken with AZACITIDINE DRL:

- if you have decreased counts of platelets, red or white blood cells.
- if you have liver problems.
- if you have kidney problems.
- if you have ever had a heart condition or heart attack or any history of lung disease.

- AZACITIDINE DRL may cause a rare infection of the deeper layers of skin and subcutaneous tissues. Tell your doctor if you notice any changes to your skin or if you develop a fever.
- AZACITIDINE DRL may cause a condition that happens when cancer cells die quickly. Dying cells release large amounts of potassium, phosphate, and uric acid into the blood. This can cause heart or kidney problems and lead to kidney failure (tumour lysis syndrome).
  Some of the symptoms are nausea, vomiting, diarrhoea, muscle cramps, numbness, seizures, confusion and weakness. This condition may be life-threatening if it is not managed or treated.
- AZACITIDINE DRL can cause a serious immune reaction called 'differentiation syndrome'.

Blood monitoring

You will have blood tests before you begin treatment with AZACITIDINE DRL and at the start of each period of treatment (called a 'cycle'). This is to check that you have enough blood cells and that your liver and kidneys are working properly.

Use in children and adolescents

AZACITIDINE DRL is not to be used to treat children and adolescents below the age of 18.

Use in elderly

Use AZACITIDINE DRL with caution in the elderly, they may be more sensitive to its effects.

Other medicines and AZACITIDINE DRL

Always tell your healthcare professional if you are taking any other medicine.

(This includes complementary or traditional medicines).

Know the medicines you take. Keep a list of them with you to show your doctor and pharmacist each time you get a new medicine.

AZACITIDINE DRL with food and drink

There is no information to suggest that food and drink consumption affects the way that AZACITIDINE DRL works.

Pregnancy, breastfeeding and fertility

- AZACITIDINE DRL may be harmful to the baby, therefore it should not be used if you are pregnant.
- If you are pregnant or breastfeeding, think you may be pregnant or plan to become pregnant consult your doctor, pharmacist or other health care professional for advice before taking

AZACITIDINE DRL.

- Tell your doctor straight away if you become pregnant during treatment.
- If you are a woman who can become pregnant you should use a highly effective method of contraception while using AZACITIDINE DRL and for 6 months after stopping treatment with AZACITIDINE DRL.
- You should not breast-feed when taking AZACITIDINE DRL**,** as it is not known if AZACITIDINE DRL passes into breast milk.
- If you are a male, you should not father a child while receiving treatment with AZACITIDINE DRL. Men should use an effective method of contraception while using AZACITIDINE DRL for 3 months after stopping treatment with AZACITIDINE DRL. You should seek counselling on sperm storage.
- Female partners of male patients receiving AZACITIDINE DRL should not become pregnant.

Driving and using machines

AZACITIDINE DRL may make you feel tired. If this happens, do not drive or operate any tools and machines.

AZACITIDINE DRL contains mannitol

AZACITIDINE DRL contains mannitol:

- which is a type of sugar, which may have an effect on the control of your blood sugar if you have diabetes mellitus.

If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before using

AZACITIDINE DRL.

- which, on rare occasions, may cause hypersensitivity reactions and may have a laxative effect.

3. How to use AZACITIDINE DRL

Your doctor will decide on the most suitable treatment for you including:

- the correct dose
- how often and for how long you should be treated and
- whether you should also receive other medicines with AZACITIDINE DRL or not.

Your doctor will give you all the necessary information on your treatment plan.

Before giving you AZACITIDINE DRL, your doctor will give you another medicine to prevent nausea and vomiting at the start of each treatment cycle.

The recommended dose is 75 mg per m^2 body surface area. Your doctor will decide your dose of AZACITIDINE DRL, depending on your general
condition, height and weight. Your doctor will check your progress and may change your dose if necessary.
AZACITIDINE DRL is given every day for one week, followed by a rest period of 3 weeks. This "treatment cycle" will be repeated every 4 weeks. You will usually receive at least 4 treatment cycles.

AZACITIDINE DRL will be given to you as a subcutaneous injection under the skin or intravenous infusion by a doctor or nurse.
The subcutaneous injection may be given under the skin on your thigh, tummy or upper arm.

The intravenous infusion will be given over a period of 10 to 40 minutes.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

If you have the impression that the effect of AZACITIDINE DRL is too strong or too weak, tell your doctor or pharmacist.

If you receive more AZACITIDINE DRL than you should

Since a healthcare professional will administer AZACITIDINE DRL to you, he/she will control the dosage. However, in the event of overdosage your doctor will manage the overdosage.

If you forget to use AZACITIDINE DRL

Since a healthcare provider will administer AZACITIDINE DRL, it is unlikely that the dose will be missed.

If you stop taking AZACITIDINE DRL

Unless your doctor instructs you to stop treatment, it is important to continue to be given AZACITIDINE DRL**.**

If you stop treatment and your original symptoms come back tell your doctor or pharmacist immediately.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. Possible side effects

AZACITIDINE DRL can have side effects.

Not all side effects reported for AZACITIDINE DRL are included in this leaflet. Should your general health worsen or if you experience any untoward effects while taking AZACITIDINE DRL, please consult your doctor, pharmacist or other health care professional for advice.

If any of the following side effects happen, stop taking AZACITIDINE DRL and tell your doctor immediately or go to the casualty department at your nearest hospital:

- Swelling of the hands, feet, ankles, face, mouth, lips, gums, tongue, throat and neck which may cause difficulty in swallowing or breathing', throat tightness, shortness of breath and wheezing, rash, "hives" (raised bumps), blisters or itching.

These are all serious side effects. This may be due to an allergic (hypersensitivity) reaction. You may need urgent medical attention or hospitalisation.

If any of the following side effects happen, tell your doctor immediately or go to the casualty department at your nearest hospital:

- Drowsiness, shaking, jaundice (yellowing of skin and white of eyes), abdominal bloating and easy bruising.

  These may be symptoms of liver failure and can be life-threatening.
- Swelling of the legs and feet, back pain, reduced passing of water, increased thirst, rapid, pulse, dizziness and nausea, vomiting or reduced appetite and feelings of confusion, restlessness or fatigue.

  These may be symptoms of kidney failure and can be life-threatening.

- A fever.

  This could be due to an infection as a result of having low levels of white blood cells, which can be life-threatening.

- Chest pain or shortness of breath which may be accompanied with a fever.

  This may be due to an infection of the lung called "pneumonia", and can be life-threatening.

- Bleeding.

  Such as blood in the stools due to bleeding in the stomach or gut.

Other side effects include:

Frequent side effects:

- An infection of the nose and throat or the common cold (nasopharyngitis).
- An infection of the blood caused by bacteria (sepsis). This may be due to low levels of white cells in your blood (neutropenic sepsis).
- Infection of the sinuses, throat, airways or lung (respiratory tract).
- An infection in your urine (urinary tract infection).
- Skin infection (cellulitis).
- Pain in the gut which can result in fever and vomiting due to inflammation of the colon (diverticulitis).
- White coating covering tongue, inner cheeks, and sometimes on the roof of your mouth, gums and tonsils (oral fungal infection).
- Inflammation of the sinuses (sinusitis).
- Sore throat (pharyngitis).
- Runny nose (rhinitis).

- A viral infection causing cold sores (herpes simplex).
- Reduced red blood count (anaemia). You may feel tired and pale.
- Reduced neutrophils (type of white blood cell count (neutropenia)). This may be accompanied by a fever (febrile neutropenia). You are also more likely to get infections.
- A reduced white blood cell count (leukopenia).
- A reduced blood platelet count (thrombocytopenia). You are more prone to bleeding and bruising.
- A reduced red cell, white cell, and platelet count (pancytopenia).
- Bone marrow failure due to the low red and white blood cell and platelet counts.
- Eating disorder (anorexia), loss of appetite, low levels of potassium in the blood (hypokalaemia), increased thirst (dehydration).
- Having trouble sleeping (insomnia), confusion, feeling anxious (anxiety).
- Dizziness, headache, bleeding inside your head (intracranial haemorrhage), fainting (syncope), feeling sleepy (somnolence), feeling tired (lethargy).
- Bleeding in the eye (eye haemorrhage), bleeding of the conjunctiva (conjunctival haemorrhage).
- High or low blood pressure (hypertension or hypotension), low blood pressure that happens when you stand up from sitting or lying down making you feel faint or dizzy (orthostatic hypotension), a solid swelling of clotted blood within the tissues (haematoma).
- Being short of breath (dyspnoea), nose bleeds (epistaxis), water/fluid in the lungs (pleural effusion), being short of breath when you move (dyspnoea exertional), pain in your throat and voice box (pharyngolaryngeal pain).
- Diarrhoea ('runny tummy'), vomiting, constipation, nausea ('feeling sick'), stomach pain, bleeding in the mouth, stomach and gut (gastrointestinal haemorrhage), bleeding from around your back

passage due to piles (haemorrhoidal haemorrhage), inflammation of the mucous membrane of the mouth (stomatitis), bleeding of the gums (gingival bleeding), indigestion (dyspepsia).

- Small red or purple spots caused by bleeding into the skin (petechiae), itching (pruritus), rash, a discoloration of the skin resulting from bleeding underneath, typically caused by bruising (ecchymosis), a rash of purple spots on the skin caused by internal bleeding from small blood vessels (purpura), hair loss (alopecia), "hives"/ itchy rash (urticaria), reddening of the skin(erythema), type of rash (rash macular).
- Joint pains (arthralgia), pain (includes back, bone and pain in extremity), muscle spasms, muscle pain (myalgia).
- Kidney failure (renal failure), blood in the urine (haematuria), increased levels of creatinine (picked up in blood tests).
- Fever (pyrexia), tiredness (fatigue), physical weakness or lack of energy (asthenia), chest pain, injection site reaction including redness, pain or a skin reaction (injection site erythema), injection site pain, bruising, swelling of clotted blood within the tissues (haematoma), hardened mass associated with inflammation (induration), rash, itching (pruritus), swelling (inflammation), discoloration, bleeding at injection site, general feeling of being unwell (malaise), chills, bleeding at the catheter site.
- Decrease in weight.

<u>Less frequent side effects:</u>

- Serious immune reaction (differentiation syndrome) that may cause fever, cough, difficulty breathing, rash, decreased urine, low blood pressure (hypotension), swelling of the arms or legs and rapid weight gain.
- Infection of the deeper layers of skin, which spreads quickly, damaging the skin and tissue, which

can be life-threatening (necrotising fasciitis).

- Allergic (hypersensitivity) reactions.
- A group of abnormalities that can occur as a complication during the treatment of cancer e.g., high levels of potassium, phosphorus, calcium, uric acid, blood urea nitrogen (BUN) and other nitrogen containing compounds (tumour lysis syndrome).
- Group of diseases affecting different parts of the lung (interstitial lung disease).
- Liver failure (hepatic failure), coma caused due to liver failure (progressive hepatic failure).
- A skin disease characterised by the sudden onset of fever, an elevated white blood cell count, and tender, red swellings on the skin (acute febrile neutrophilic dermatosis).
- An accumulation of acid in the body due to a failure of the kidneys to (renal tubular acidosis), "death" of the skin at the injection site (injection site necrosis).

If you notice any side effects not on this leaflet, please inform you doctor or pharmacist.

Reporting of side effects

If you get side effects, talk to your doctor, pharmacist, or nurse. You can also report side effects to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

By reporting side effects, you can help provide more information on the safety of AZACITIDINE DRL.

5. How to store AZACITIDINE DRL

Unopened vial:

Store at or below 25 °C.

Reconstituted suspension for subcutaneous administration:

When reconstituted with refrigerated (2 °C to 8 °C) water for injections, the reconstituted suspension can be kept in the refrigerator (2 °C to 8 °C) for a maximum of 22 hours.

After removal from refrigerated conditions, the suspension may be allowed to equilibrate to room temperature (25 °C) for up to 30 minutes prior to administration.

Reconstituted suspension for intravenous administration:

When stored at 25 °C, the reconstituted product should be administered within 1 hour.

Discard any unused solution.

Do not dispose medicines in drains or sewerage systems (e.g., toilets).

Return all unused and expired medicines to your pharmacist.

Keep all medicines out of reach and sight of children.

6. Contents of the pack and other information

What AZACITIDINE DRL contains

The active substance is azacitidine.

Each vial contains 100 mg azacitidine.

The reconstituted suspension contains 25 mg/ml azacitidine.

The other ingredients are mannitol, nitrogen and water for injection.

What AZACITIDINE DRL looks like and contents of the pack

AZACITIDINE DRL: white to off-white sterile lyophilised powder.

30 ml USP type I flint tubular glass vial, with a 20 mm dark grey bromobutyl rubber stopper and sealed with 20 mm violet coloured aluminium flip-off tear seal.

Holder of Certificate of Registration

Dr. Reddy's Laboratories (Pty) Ltd.

Block B, 204 Rivonia Road

Morningside

Sandton

2057

This leaflet was last revised in

TBA

Registration number

51/26/0144

For any information about this medicine, please contact the local representative of the Holder of Certificate of Registration:

Dr. Reddy's Laboratories (Pty) Ltd. Tel: +27 11 324 2100

Other sources of information

Detailed information on this medicine is available on the Dr. Reddy's Laboratories web site:

http://www.drreddys.co.za