DR. REDDY'S LABORATORIES (PTY) LTD.
APPROVED PROFESSIONAL INFORMATION:
AZACITIDINE DRL (lyophilised powder for injection)

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

AZACITIDINE DRL lyophilised powder for injection.

The reconstituted suspension contains 25 mg/ml azacitidine.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg azacitidine.

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 patients with myelodysplastic syndromes including the following subtypes of the French-American- British classification:

- refractory anaemia or refractory anaemia with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia or requiring transfusions),
- refractory anaemia with excess blasts,
- refractory anaemia with excess blasts in transformation,
- and chronic myelomonocytic leukaemia.

4.2 Posology and Method of Administration

Posology

The recommended starting dose is 75 mg/m^2 subcutaneously, daily for seven (7) days, every four (4) weeks.

Patients should be premedicated with anti-emetics for nausea and vomiting.

The dose may be increased to 100 mg/m^2 if no beneficial effect is seen after two (2) treatment cycles and if no toxicity except for nausea and vomiting has occurred. It is recommended that patients be treated for a minimum of four (4) cycles. However, complete and partial response may require more than four (4) treatment cycles. Treatment may continue for as long as the patient continues to benefit.

Patients should be monitored for haematologic response and renal toxicities, and dosage delay or reduction as described below may be necessary.

Dose adjustment based on Haematology Laboratory Values:

- For patients with baseline (start of treatment) WBC ≥ 3,0 x 10^9/l, ANC ≥ 1,5 x 10^9/l, and platelets ≥ 75,0 x 10^9/l, adjust the dose as follows, based on the nadir counts for any given cycle:

Nadir Counts		**% Dose in the Next Course**
ANC (10 ^{9}/l)	*Platelets (10 ^{9}/l)*	
< 0,5	< 25,0	50 %
0,5 – 1,5	25,0 – 50, 0	67 %
> 1,5	> 50,0	100 %

- For patients whose baseline counts are WBC < 3,0 x 10^9/l, ANC < 1,5 x 10^9/l, or platelets < 75,0 x 10^9/l, dose adjustments should be based on nadir counts and bone marrow biopsy cellularity at the time of the nadir as noted below, unless, there is clear improvement in differentiation (percentage of mature granulocytes is higher and ANC is higher than at onset of that course) at the time of the next cycle, in which case the dose of the current treatment should be continued.

WBC or Platelet Nadir % decrease in counts from baseline	**Bone Marrow Biopsy Cellularity at Time of Nadir (%)**		
	30 - 60	**15 - 30**	**< 15**
	% Dose in the Next Course		
50 - 75	100	50	33
> 75	75	50	33

Dosage Adjustment Based on Renal Function and Serum Electrolytes:

If unexplained elevations of 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 course.

Similarly, if unexplained reductions in serum bicarbonate levels to less than 20mmol/l occur, the dosage should be reduced by 50 % on the next course.

Special Populations:

Patients with Renal Impairment:

No studies have been conducted in MDS patients with decreased renal function. Since AZACITIDINE DRL and its metabolites are primarily excreted by the kidneys, patients with renal impairment should be monitored closely and the dose adjusted as described.

Patients with Hepatic Impairment:

No studies have been conducted in MDS patients with hepatic impairment. Since AZACITIDINE DRL may be metabolised in the liver and is potentially hepatotoxic in patients with severe pre-existing hepatic impairment caution is needed in patients with liver disease.

Elderly:

AZACITIDINE DRL and its metabolites are known to be substantially excreted by the kidney, and the risk of toxic reactions to AZACITIDINE DRL may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Children:

The safety and efficacy of AZACITIDINE DRL in children and adolescents under 18 years of age has not been established.

Laboratory tests

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

Method of Administration:

AZACITIDINE DRL should be administered under the supervision of a medical practitioner qualified in the use of anticancer agents.

Reconstituted AZACITIDINE DRL should be injected subcutaneously. Rotate sites for injection (thigh, abdomen, or upper arm). New injections should be given at least one inch

from an old site and never into areas where the site is tender, bruised, red or hard.

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).

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. 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

It was reported that in patients treated with intravenous azacitidine, in combination with other chemotherapeutic agents, renal abnormalities ranging from elevated serum creatinine to renal failure and death have occurred. In addition, renal tubular acidosis, which is the 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 patients 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 doctor immediately. Even though no clinically relevant differences in the frequency of adverse reactions were noted between subjects with normal renal function compared to those with renal impairment, patients with renal impairment should be closely monitored for toxicity since azacitidine and/or its metabolites are primarily excreted by the kidney.

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.

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.

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 P 450 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 and men have to use effective contraception during and up to 3 months after treatment.

Pregnancy

Women of childbearing potential should be advised to avoid falling pregnant while taking AZACITIDINE DRL.

Since safety has not been demonstrated in pregnant women, AZACITIDINE DRL should not be used in pregnancy. If the patient does become pregnant then patient should be informed about the potential hazard to the foetus.

The advantage of treatment should be weighed against the potential risk for the foetus in every individual case.

Lactation

It is not known whether AZACITIDINE DRL or its metabolites are excreted in human milk. 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. Men should be advised not to father a child while receiving treatment and must use effective contraception during and up to 3 months after treatment. 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 has minor or moderate influence on the ability to drive and use machines. Caution is recommended when driving or operating machines, as fatigue has been reported with the use of AZACITIDINE DRL.

4.8 Undesirable effects

The most commonly reported adverse reactions were gastrointestinal (nausea, vomiting

and diarrhoea), haematological (anaemia, thrombocytopenia, leukopenia/neutropenia), and injection site reactions (erythema and pain). In general, these events reflect the underlying nature of the disease and that AZACITIDINE DRL is cytotoxic. No clinically significant differences were seen when the safety data were analysed for age, gender or MDS subtypes.

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		necrotising fasciitis *
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 commonly reported (≥ 10 %) haematological adverse reactions associated with azacitidine treatment include anaemia, thrombocytopenia, neutropenia, febrile neutropenia and leukopenia, and were usually Grade 3 or 4. 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. None of these adverse reactions led to discontinuation of azacitidine, or reduction of azacitidine dose in the pivotal studies. 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, rash, erythema and skin lesion may require management with concomitant medicinal products, such as antihistamines, corticosteroids and non-steroidal anti-inflammatory medicinal products (NSAIDs). These cutaneous reactions have to be distinguished from soft tissue infections, sometimes occurring at injection site. Soft tissue infections, including cellulitis

and necrotising fasciitis in rare cases leading to death, have been reported with azacitidine in the post marketing setting. For clinical management of infectious adverse reactions, see section 4.8 Infections.

Gastrointestinal adverse reactions

The most commonly 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 and haematuria 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 hepatic failure, 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 a statistically significant 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 (with 14 [5,9 %] patients ≥ 85 years in AZA-AML-001 study).

<u>Reporting of suspected adverse reactions</u>

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 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

In the event of an overdose, 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 Cytostatics

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

Mechanism of action

It is believed that azacitidine exerts its antineoplastic effects by multiple mechanisms including direct cytotoxicity on abnormal haematopoietic cells in the bone marrow and hypomethylation of DNA. The cytotoxic effects of azacitidine may result from inhibition of DNA, RNA and protein synthesis; the incorporation into RNA and DNA; and the activation of DNA damage pathways. Non- proliferating cells are relatively insensitive to azacitidine. When azacitidine is incorporated into DNA then the inactivation of DNA methyltransferase leading to hypomethylation of DNA takes place. DNA hypomethylation of aberrantly methylated genes involved in normal cell cycle regulation, differentiation and death pathways may result in gene re-expression and restoration of cancer-suppressing

functions to cancer cells. The relative importance of DNA hypomethylation versus cytotoxicity or other activities of azacitidine to clinical outcomes has not been established.

5.2 Pharmacokinetic properties

Absorption:

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

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).

The mean plasma half- life ($t_{½}$) after subcutaneous injection is approximately 41 ± 8 minutes. 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.

Distribution:

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

Biotransformation:

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).

Azacitidine undergoes spontaneous hydrolysis and deamination mediated by cytidine deaminase. In human liver S9 fractions, formation of metabolites was independent of

NADPH implying that azacitidine metabolism was not mediated by cytochrome P450 isoenzymes.

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.

Elimination:

Azacitidine is rapidly cleared from plasma with a mean elimination half-life ($t_{½}$) after subcutaneous administration of 41 ± 8 minutes. No accumulation occurs after subcutaneous administration of 75 mg/m^2 azacitidine once daily for 7 days. The primary route of elimination of azacitidine and/or its metabolites is through urinary excretion. Following intravenous and subcutaneous administration of ^{14}C-azacitidine, 85 and 50 % of the administered radioactivity was recovered in urine respectively and < 1 % was recovered in faeces.

Special Populations

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

Renal impairment:

After single and multiple subcutaneous administrations of azacitidine, renal impairment had no major effect on the pharmacokinetic exposure thereof.

Following subcutaneous administration of a single 75 mg/m^2 dose, mean exposure values (AUC and C_{max}) from subjects with mild, moderate and severe renal impairment were increased by 11 to 21 %, 15 to 27 %, and 41 to 66 %, respectively, compared to normal renal function subjects. However, exposure was within the same general range of exposures observed for subjects with normal renal function. Provided renally impaired patients are monitored for toxicity, azacitidine can be administered to these patients without initial dose adjustment. Azacitidine and/or its metabolites are primarily excreted by the kidney.

Pharmacogenomics

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

5.3 Preclinical safety data

Azacitidine induces both gene mutations and chromosomal aberrations in bacterial and mammalian cell systems *in vitro*. The potential carcinogenicity of azacitidine was evaluated in mice and rats. Azacitidine induced tumours of the haematopoietic system in female mice, when administered intraperitoneally 3 times per week for 52 weeks. An increased incidence of tumours in the lymphoreticular system, lung, mammary gland, and skin was seen in mice treated with azacitidine administered intraperitoneally for 50 weeks. A tumorigenicity study in rats revealed an increased incidence of testicular tumours.

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 powder vial:

2 years

Reconstituted suspension:

Store up to 1 hour at 25 °C or up to 8 hours between 2 °C and 8 °C.

If administration is to be delayed, the reconstituted product may be kept in the vial or drawn into a syringe. The product must be refrigerated (2 to 8 °C) immediately. 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. When stored at 25 °C, the reconstituted product should be administered within 1 hour.

The shelf life of the reconstituted product can be extended by reconstituting with refrigerated (2 °C to 8 °C) water for injections.

When AZACITIDINE DRL is reconstituted using refrigerated (2 °C to 8 °C) water for injections, the chemical and physical in-use stability of the reconstituted medicinal product has been demonstrated at 2 °C to 8 °C for 22 hours.

Discard any unused solution.

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 medicinal product and, therefore caution should be exercised when handling and preparing AZACITIDINE DRL suspensions.

Procedures for proper handling and disposal of anticancer medicinal products 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.

Reconstitution procedure

AZACITIDINE DRL should be reconstituted with water for injection. The shelf life of the reconstituted medicinal product can be extended by reconstituting with refrigerated (2 °C to 8 °C) water for injection.

Details on storage of the reconstituted product are provided below.

1. AZACITIDINE DRL should be reconstituted aseptically with 4 ml of water for injection.

2. The needle of the syringe containing the 4 ml of water for injection should be inserted through the rubber top of the AZACITIDINE DRL vial followed by injection of the water for injection into the vial.

3. After removing the syringe and needle the vial should be vigorously shaken until a uniform cloudy suspension is achieved. After reconstitution each ml of suspension will contain 25 mg of azacitidine (100 mg/4 ml). The reconstituted product is a homogeneous, cloudy suspension, free of agglomerates. The product should be discarded if it contains large particles or agglomerates. Do not filter the suspension after reconstitution since this could remove the active substance. It must be taken into account that filters are present in some adaptors, spikes and closed systems; therefore, such systems should not be used for administration of the medicinal product after reconstitution.

4. The rubber top should be cleaned and a new syringe with needle inserted into the vial. The vial should then be turned upside down, making sure the needle tip is below the level of the liquid. The plunger should then be pulled back to withdraw the amount of AZACITIDINE DRL required for the proper dose, making sure to purge any air trapped within the syringe. The syringe with needle should then be removed from the vial and the needle disposed of.

5. A fresh subcutaneous needle (recommended 25-gauge) should then be firmly attached to the syringe. The needle should not be purged prior to injection, in order to reduce the incidence of local injection site reactions.

6. If needed (doses over 100 mg) all the above steps for preparation of the suspension should be repeated. For doses greater than 100 mg (4 ml), the dose should be equally divided into 2 syringes (e.g., dose 150 mg = 6 ml, 2 syringes with 3 ml in each syringe).

7. The contents of the dosing syringe must be re-suspended immediately prior to administration. The syringe filled with reconstituted suspension should be allowed up to 30 minutes prior to administration to reach a temperature of approximately 20 °C to 25 °C. If the elapsed time is longer than 30 minutes, the suspension should be discarded appropriately and a new dose prepared. To re-suspend, vigorously roll the syringe between the palms until a uniform, cloudy suspension is achieved. The product should be discarded if it contains large particles or agglomerates.

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

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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

08 June 2021