1.3.1 SOUTH AFRICAN PACKAGE INSERT

1.3.1.1 PACKAGE INSERT HUMAN MEDICINE

SCHEDULING STATUS: S4

1. NAME OF MEDICINE

SPALZACT 100 mg (Powder for suspension for Injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg azacitidine. The reconstituted suspension contains 25 mg/ml azacitidine.

Contains sugar (mannitol 100 mg / vial)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

SPALZACT 100 is a white to off-white, sterile lyophilised powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

SPALZACT 100 is indicated for 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 days, every four weeks. Patients should be premedicated for nausea and vomiting. The dose may be increased to 100 mg/m^2 if no beneficial effect is seen after two treatment cycles and if no toxicity other than nausea and vomiting has occurred. It is recommended that patients be treated for a minimum of 4 cycles. However, complete or partial response may require more than 4 treatment cycles. Treatment may be continued 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.

Dosage Adjustment based on Haematology Laboratory Values:

For patients with baseline (start of treatment) WBC ≥ 3,0 x10^9/L, ANC ≥ 1,5x10^9/L, and platelets ≥ 75,0 x10^9/L, adjust the dose as follows, based on nadir counts for any given cycle:

Nadir Counts		% Dose in the Next Course
ANC (x10^9/L)	Platelets (x10^9/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 x10^9/L, ANC < 1,5 x10^9/L, or platelets < 75,0 x10^9/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 20 mmol/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 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 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 and its metabolites are known to be substantially excreted by the kidney, and the risk of toxic reactions to SPALZACT 100 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.

Paediatric Population:

The safety and efficacy of SPALZACT 100 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:

SPALZACT 100 should be administered under the supervision of a medical practitioner qualified in the use of anticancer medicines.

Reconstituted SPALZACT 100 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 were the site is tender, bruised, red, or hard.

4.3 Contraindications

SPALZACT 100 is contraindicated in the following:

- patients with known hypersensitivity to SPALZACT 100 (azacitidine) or to any of the excipients (see section 6.1).
- patients with advanced malignant hepatic tumours.

4.4 Special warnings and precautions for use

Haematological toxicity

Treatment with SPALZACT 100 is associated with anaemia, neutropenia and thrombocytopenia, particularly during the first 2 cycles (see section 4.8). Complete blood counts should be performed as needed to monitor response and toxicity, but at least prior to each treatment cycle. 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 medical practitioners are also advised to be observant for signs and symptoms of bleeding.

Hepatic impairment

No formal studies have been conducted in patients with hepatic impairment. Patients with extensive tumour burden due to metastatic disease have been reported to experience progressive hepatic coma and death during SPALZACT 100 treatment, especially in such

patients with baseline serum albumin < 30 g/L. SPALZACT 100 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 SPALZACT 100 in combination with other chemotherapeutic medicines. 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 subjects with chronic myelogenous leukaemia (CML) treated with azacitidine and etoposide. If unexplained reductions in serum bicarbonate (< 20 mmol/L) or elevations of serum creatinine or BUN occur, the dose should be reduced or administration delayed (see section 4.2). Patients should be advised to report oliguria and anuria to the health care provider immediately. Patients with renal impairment should be closely monitored for toxicity and the dose adjusted as described 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 also section 4.8.

Cardiac and pulmonary disease

Patients with a history of severe congestive heart failure, clinically unstable cardiac disease or pulmonary disease were excluded from the pivotal registration studies (AZA PH GL 2003 CL 001 and AZA-AML-001) and therefore the safety and efficacy of azacitidine in these patients has not been established. Recent data from a clinical trial in patients with a known history of cardiovascular or pulmonary disease showed a significantly increased incidence of cardiac events with azacitidine (see section 4.8). It is therefore advised to exercise caution

when prescribing azacitidine to these patients. Cardiopulmonary assessment before and during the treatment should be considered.

Necrotising fasciitis

Necrotising fasciitis, including fatal cases, have been reported in patients treated with SPALZACT 100. SPALZACT 100 therapy 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.

Other

Men should be advised not to father a child while receiving treatment with SPALZACT 100.

4.5 Interaction with other medicines and other forms of interaction

Medicine interaction studies with azacitidine have not been conducted.

An in vitro study of azacitidine incubation in human liver fractions indicated that azacitidine may be metabolised by the liver. Whether azacitidine metabolism may be affected by known microsomal enzyme inhibitors or inducers has not been studied.

In vitro studies of azacitidine with human cultured hepatocytes indicate that azacitidine at concentrations of 1,0 µM to 100 µM does not induce CYP 1A2, 2C19, or 3A4/5.

The potential of azacitidine to inhibit cytochrome P450 (CYP) enzymes is not known.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential:

Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with SPALZACT 100.

Pregnancy:

Safety in pregnancy and lactation has not been established.

There are no adequate data on the use of SPALZACT 100 in pregnant women. Studies in

animals have shown reproductive toxicity. The potential risk for humans is unknown.

SPALZACT 100 should not be used during pregnancy.

If the patient becomes pregnant while taking SPALZACT 100, the patient should be informed of the potential hazard to the fetus.

Lactation:

It is not known whether azacitifine or its metabolites are excreted in human milk.

Because of the potential for tumorigenicity shown for azacitifine in animal studies and the potential for serious adverse reactions, women treated with SPALZACT 100 should not breast feed.

Fertility

There are no human data on the effect of azacitidine on fertility.

4.7 Effects on ability to drive and use machines

Azacitidine has minor or moderate influence on the ability to drive and use machines. Fatigue has been reported with the use of azacitidine, as contained in SPALZACT 100.Therefore, caution is recommended when driving or operating machines.

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 SPALZACT 100 is cytotoxic.

No clinically significant differences were seen when the safety data were analysed for age, gender or MDS subtypes.

Adverse reactions reported in more than an isolated case are listed below in patients treated with azacitidine as contained in SPALZACT 100 by system organ class and by frequency.

System Organ Class	Frequent	Less Frequent	Frequency unknown
Blood and lymphatic system disorders	febrile neutropenia*, neutropenia, leukopenia, thrombocytopenia, anaemia, pancytopenia*, bone marrow failure		
Eye disorders	eye haemorrhage, conjunctival haemorrhage		
Cardiac disorders	pericardial effusion	pericarditis	
Gastrointestinal disorders	diarrhoea, vomiting, constipation, nausea, abdominal pain (includes upper and abdominal discomfort), gastrointestinal haemorrhage* (includes mouth haemorrhage), haemorrhoidal haemorrhage, stomatitis, gingival bleeding, dyspepsia		

General disorders and administrative 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)	
Hepatobiliary disorders		hepatic failure*, progressive hepatic coma	
Immune system disorders		medicine hypersensitivity	
Infections and infestations	nasopharyngitis, pneumonia, upper respiratory tract infection, 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 *
Injury, poisoning and procedural complications		post procedural haemorrhage	

Investigations	weight decreased		
Metabolic and nutrition disorders	Anorexia, decreased appetite, hypokalemia, dehydration	tumour lysis syndrome	
Musculoskeletal, and connective tissue disorders	arthralgia, myalgia, muscle spasms		
Nervous system disorders	Dizziness, headache, intracranial haemorrhage*, syncope, somnolence, lethargy		
Psychiatric disorders	anxiety, insomnia, confusional state		
Renal and urinary disorders	renal failure*, haematuria, elevated serum creatinine	renal tubular acidosis	
Respiratory, thoracic and mediastinal disorders	dyspnoea, epistaxis, pleural effusion, dyspnoea exertional, pharyngolaryngeal pain	interstitial lung disease	
Skin and subcutaneous tissue disorders	petechiae, pruritus (includes generalized), rash, ecchymosis, purpura, alopecia, urticaria, erythema, rash macular	acute febrile neutrophilic dermatosis, pyoderma gangrenosum	
Vascular disorders	hypotension*, hypertension, orthostatic hypotension, haematoma		

* = 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 Infections above.

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.

Reporting of suspected adverse reactions

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

4.9 Overdose

In the event of overdosage, the patient should be monitored with appropriate blood counts and should receive supportive treatment, as necessary. There is no known specific antidote for SPALZACT 100 overdosage.

One case of overdose with azacitidine was reported during clinical trials. A patient experienced diarrhoea, nausea, and vomiting after receiving a single IV dose of approximately 290 mg/m^2, almost 4 times the recommended starting dose. The events resolved without sequelae, and the correct dose was resumed the following day.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 26 – Cytostatics

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

Azacitidine is believed to exert its antineoplastic effects by causing hypomethylation of

DNA and direct cytotoxicity on abnormal haematopoietic cells in the bone marrow. The concentration of azacitidine required for maximum inhibition of DNA methylation in vitro does not cause major suppression of DNA synthesis. Hypomethylation may restore normal function to genes that are critical for differentiation and proliferation. The cytotoxic effects of azacitidine cause the death of rapidly dividing cells including cancer cells that are no longer responsive to normal growth control mechanisms. Non-proliferating cells are relatively insensitive to azacitidine.

5.2 Pharmacokinetic properties

The pharmacokinetics of azacitidine were studied in six MDS patients following a single 75 mg/m^2 SC and a single 75 mg/m^2 intravenous (IV) dose. Azacitidine was rapidly absorbed after SC administration: the peak plasma azacitidine concentration of 750 ± 403 ng/mL occurred in 0,5 hour. The bioavailability of SC azacitidine relative to IV azacitidine was approximately 89 % based on area under the curve. Mean volume of distribution following IV dosing was 76 ± 26 L. Mean apparent SC clearance was 167 ± 49 L/hr, and mean half-life after SC administration was 41 ± 8 minutes.

An in vitro study of azacitidine incubation in human liver fractions indicated that azacitidine may be metabolised by the liver. Whether azacitidine metabolism may be affected by known microsomal enzyme inhibitors or inducers has not been studied. In vitro studies of azacitidine with human cultured hepatocytes indicate that azacitidine at concentrations of 1,0 µM to 100 µM does not induce CYP 1A2, 2C19, or 3A4/5.

Published studies indicate that urinary excretion is the primary route of elimination of azacitidine and its metabolites. Following IV administration of radioactive azacitidine to 5 cancer patients, the cumulative urinary excretion was 85 % of the radioactive dose.

Faecal excretion accounted for < 1 % of administered radioactivity over three days. Mean excretion of radioactivity in urine following SC administration of ^{14}C-azacitidine was 50 %. The mean elimination half-lives of total radioactivity (azacitidine and its

metabolites) were similar after IV and SC administrations, about 4 hours.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol, pyrogen free

Water for injection

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 4.2.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25 °C.

Do not freeze. Store in the original package to protect from moisture.

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

If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and must not be longer than 8 hours at 2 °C to 8 °C when reconstituted using water for injections that has not been refrigerated or not longer than 22 hours when reconstituted using refrigerated (2 °C to 8 °C) water for injections.

KEEP OUT OF REACH OF CHILDREN.

6.5 Nature and contents of container

Clear single use Type I glass vial sealed with 20 mm grey bromobutyl rubber stopper and white coloured flip off seals.

6.6 Special precautions for disposal and other handling

Recommendations for safe handling:

SPALZACT 100 is a cytotoxic medicine and caution should be exercised when handling and preparing SPALZACT 100 suspensions. Procedures for proper handling and disposal of anticancer medicines should be applied.

If reconstituted SPALZACT 100 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:

SPALZACT 100 should be reconstituted aseptically with 4 ml sterile water for injection. The diluent should be injected slowly into the vial. Vigorously shake or roll the vial until a uniform suspension is achieved. The suspension will be cloudy. The resulting suspension will contain azacitidine 25 mg/ml.

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

Doses greater than 4 ml should be divided equally into two syringes and injected into two separate sites. To provide a homogeneous suspension, the contents of the syringe must be re-suspended by inverting the syringe 2–3 times and vigorously rolling the syringe between the palms for 30 seconds immediately prior to administration.

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.

Preparation for delayed administration:

The reconstituted product may be kept in the vial or drawn into a syringe. The product must be refrigerated (2 ºC – 8 ºC) immediately. 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.

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

7 HOLDER OF CERTIFICATE OF REGISTRATION

Ruby Pharmaceuticals (PTY) LTD

Unit 1, 96 Hartley Road

Durban. 4091

8 REGISTRATION NUMBER(S)

55/26/0559

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10 DATE OF REVISION OF THE TEXT