PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

AZATURAS 25 mg/mL, powder for suspension 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:

Contains sugar (mannitol): 100 mg per vial.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for suspension for injection.

White lyophilised powder.

The pH of the 4 mL reconstituted suspension is between 5,0 and 8,0.

The osmolality ratio is between 0,8 and 1,2 mOsmol/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AZATURAS 25 mg/mL is indicated for treatment of patients with myelodysplastic syndromes (MDS) including the following subtypes of the French-American-British classification:

- Refractory anaemia (RA) 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 – 30 % bone marrow blasts and multilineage dysplasia according to World Health Organisation (WHO) classification).
- AZATURAS 25 mg/mL is also indicated for treating adult patients with chronic myelomonocytic leukaemia (CMML) according to the FAB system.

4.2 Posology and method of administration

Posology

AZATURAS 25 mg/mL treatment should be initiated and monitored under the supervision of a medical practitioner experienced in the use of chemotherapeutic medicine. Patients should be premedicated with anti-emetics for nausea and vomiting.

The recommended starting dose for the first treatment cycle, for all patients regardless of baseline haematology laboratory values, is 75 mg/m^2 of body surface area, daily for 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 haematological 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.

Laboratory tests

Liver chemistries and serum creatinine should be obtained 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 dosing cycle (see section 4.4).

Dosage adjustments 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 x 10^9/L, and platelets > 75,0 x 10^9/L). If haematological toxicity is observed following AZATURAS 25 mg/mL treatment, the next cycle of AZATURAS 25 mg/mL 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 (x 10^9/L)	Platelets (x 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 x 10^9/L

Following AZATURAS 25 mg/mL 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 AZATURAS 25 mg/mL 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 cellularity	% Dose in the next cycle, if recovery is not achieved within 14 days	
	Recovery* ≤ 21 days	Recovery > 21 days
15 – 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

AZATURAS 25 mg/mL can be administered to patients with renal impairment without initial dose adjustments.

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.

Patients with hepatic impairment

No studies have been conducted in patients with hepatic impairment.

AZATURAS 25 mg/mL is contraindicated in patients with malignant hepatic tumours (see sections 4.3 and 4.4).

Elderly patients

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

The safety and efficacy of AZATURAS 25 mg/mL in children and adolescents under 18 years of age has not been established.

Method of administration

Reconstituted AZATURAS 25 mg/mL should be injected subcutaneously.

Rotate sites for injection (thigh, abdomen, or upper arm). 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.

For instructions on reconstitution of the medicine before administration, see section 6.6.

4.3 Contraindications

AZATURAS 25 mg/mL is contraindicated in the following:

- Patients with known hypersensitivity to azacitidine or to any of the excipients listed in section 6.1.
- Patients with malignant hepatic tumours (see section 4.4).
- Pregnancy and breastfeeding (see section 4.6).
- Patients must not receive live vaccines while being treated with AZATURAS 25 mg/mL.
- AZATURAS 25 mg/mL 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 AZATURAS 25 mg/mL is associated with anaemia, neutropenia and thrombocytopenia, particularly during the first 2 cycles. 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 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 (see section 4.2, “Laboratory tests”).

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 AZATURAS 25 mg/mL treatment, especially in such patients with baseline serum albumin < 30 g/L (see section 4.2, “Special populations”). AZATURAS 25 mg/mL is contraindicated in patients with 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 AZATURAS 25 mg/mL 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 subjects with chronic myelogenous leukaemia (CML) treated with azacitidine and etoposide (see section 4.2, “Special populations”). If unexplained reductions in serum bicarbonate (< 20 mmol/L) or elevations of serum creatinine or BUN occur, the dosage should be reduced or administration delayed. Patients should be advised to report oliguria and anuria to the healthcare professional immediately. Patients with renal impairment should be closely monitored for toxicity, since AZATURAS 25 mg/mL and/or its metabolites are primarily excreted by the kidneys (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 sections 4.8 and 4.2.

Cardiac and pulmonary disease

Patients with a history of severe congestive heart failure, clinically unstable cardiac disease or pulmonary disease were excluded from the clinical studies and therefore the safety and efficacy of azacitidine in these patients have not been established. 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 azacitidine. AZATURAS 25 mg/mL 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.

Differentiation syndrome

Cases of differentiation syndrome (also known as retinoic acid syndrome) have been reported in patients receiving injectable azacitidine. 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.

4.5 Interaction with other medicines and other forms of interaction

Based on *in vitro* data, azacitidine metabolism does not appear to be mediated by cytochrome P450 isoenzymes (CYPs), UDP-glucuronosyltransferases (UGTs), sulphotransferases (SULTs) and glutathione transferases (GSTs); interactions related to these metabolising enzymes *in vivo* are therefore considered unlikely.

Clinically significant inhibitory or inductive effects of azacitidine on cytochrome P450 enzymes are unlikely (see section 5.2).

No formal clinical medicine interaction studies with azacitidine have been conducted.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / contraception in males and females

Women of childbearing potential should be advised to avoid pregnancy during treatment with AZATURAS 25 mg/mL and should use effective contraception during and up to 3 months after treatment.

Pregnancy

AZATURAS 25 mg/mL is contraindicated in pregnancy (see section 4.3).

AZATURAS 25 mg/mL may cause foetal harm when administered to a pregnant woman.

Azacitidine was teratogenic in animals. If AZATURAS 25 mg/mL is used during pregnancy or if a patient becomes pregnant while receiving AZATURAS 25 mg/mL, the patient should be apprised of the potential hazard to the foetus.

Female partners of male patients receiving AZATURAS 25 mg/mL should not become pregnant.

Breastfeeding

Due to the potential serious adverse reactions in the nursing child, breastfeeding is contraindicated during azacitidine therapy.

Fertility

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

AZATURAS 25 mg/mL has minor or moderate influence on the ability to drive and use machines. Fatigue has been reported with the use of AZATURAS 25 mg/mL. Therefore, caution is recommended when driving or operating machines.

4.8 Undesirable effects

a. 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 (erythema and pain). In general, these events reflect the underlying nature of the disease and that AZATURAS 25 mg/mL is cytotoxic.

b. Tabulated summary of adverse reactions

Post-marketing adverse reactions not seen in clinical trials are also included.

SYSTEM ORGAN CLASS	**FRQUENCY**	**ADVERSE REACTIONS**
Infections and infestations	Frequent:	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

SYSTEM ORGAN CLASS	**FRQUENCY**	**ADVERSE REACTIONS**
	Frequency unknown:	necrotising fasciitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Frequency unknown:	differentiation syndrome (see section 4.4)
Blood and lymphatic system disorders	Frequent:	febrile neutropenia*, neutropenia, leukopenia, thrombocytopenia, anaemia, pancytopenia*, bone marrow failure, lymphadenopathy
	Less frequent:	agranulocytosis
Immune system disorders	Less frequent:	hypersensitivity reactions
Metabolism and nutrition disorders	Frequent:	anorexia, decreased appetite, hypokalaemia, dehydration
	Less frequent:	tumour lysis syndrome
Psychiatric disorders	Frequent:	insomnia, confusional state, anxiety
Nervous system disorders	Frequent:	dizziness, headache, intracranial haemorrhage*, syncope, somnolence, lethargy, burning sensation, hypaesthesia
Eye disorders	Frequent:	eye haemorrhage, conjunctival haemorrhage
Cardiac disorders	Frequent:	pericardial effusion
	Less frequent:	pericarditis
Vascular disorders	Frequent:	hypotension*, hypertension, orthostatic hypotension, haematoma, flushing, petechiae

SYSTEM ORGAN CLASS	**FRQUENCY**	**ADVERSE REACTIONS**
Respiratory, thoracic and mediastinal disorders	Frequent:	dyspnoea*, epistaxis, pleural effusion, exertional dyspnoea, pharyngolaryngeal pain, pharyngitis, haemoptysis, nasal congestion
	Less frequent:	interstitial lung disease
Gastrointestinal disorders	Frequent:	diarrhoea, vomiting, constipation, nausea, abdominal pain (includes upper and abdominal discomfort), gastrointestinal haemorrhage* (includes mouth haemorrhage), haemorrhoidal haemorrhage, stomatitis, gingival bleeding, dyspepsia, loose stools, oral mucosal petechiae, tongue ulceration
	Less frequent:	perirectal abscess
Hepatobiliary disorders	Less frequent:	hepatic failure*, progressive hepatic coma
Skin and subcutaneous tissue disorders	Frequent:	petechiae, pruritus (includes generalised), rash, ecchymosis, purpura, alopecia, urticaria, erythema, macular rash, increased sweating rash
	Less frequent:	acute febrile neutrophilic dermatosis, pyoderma gangrenosum
Musculoskeletal and connective tissue disorders	Frequent:	arthralgia, musculoskeletal pain (includes back, bone and pain in extremity), muscle spasms, myalgia
Renal and urinary	Frequent:	renal failure*, haematuria, elevated serum

disorders		creatinine, dysuria
	Less frequent:	renal tubular acidosis
General disorders and administration site conditions	Frequent:	pyrexia*, fatigue, asthenia, chest pain, injection site erythema, injection site pain, injection site reaction (unspecified), bruising, haematoma, induration, rash, pruritus, inflammation, discolouration, nodule and haemorrhage (at injection site), malaise, chills, catheter site haemorrhage, rigors
	Less frequent:	injection site necrosis
Investigations	Frequent:	decreased body mass, increased blood creatinine
Injury, poisoning and procedural complications	Frequent:	post-procedural haemorrhage

* = rarely fatal cases have been reported.

c. Description of selected adverse reactions

Haematological adverse reactions

The most frequently reported 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 lower 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 of treatment 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 medicines, such as antihistamines, corticosteroids and nonsteroidal anti-inflammatory medicines (NSAIDs). These cutaneous reactions have to be distinguished from soft tissue infections, sometimes occurring at the 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 and infestations”.

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, antidiarrhoeals, and laxatives and/or stool softeners.

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 study 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).

e. Other special populations

Elderly patients

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of AZATURAS 25 mg/mL is important. It allows continued monitoring of the benefit/risk balance of AZATURAS 25 mg/mL. Health care providers are requested to report any suspected adverse 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 overdosage, the patient should be monitored with appropriate blood counts and should receive supportive treatment, as necessary. There is no known specific antidote for AZATURAS 25 mg/mL overdosage.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 26 Cytostatic agents.

Pharmacotherapeutic group: Antineoplastic agents, pyrimidine analogues.

ATC code: L01BC07.

Mechanism of action

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. Nonproliferating cells are relatively insensitive to azacitidine.

5.2 Pharmacokinetic properties

Absorption

Following subcutaneous administration of a single 75 mg/m^2 dose, azacitidine was rapidly absorbed with peak plasma concentrations of 750 ± 403 ng/mL occurring at 0,25 h after dosing (the first sampling point). The absolute bioavailability of azacitidine after subcutaneous relative to intravenous administration (single 75 mg/m^2 doses) was approximately 89 % based on the area under the curve (AUC).

Area under the curve 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 147 ± 47 L/h.

Biotransformation

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

Elimination

Azacitidine is cleared rapidly 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.

Urinary excretion is the primary route of elimination of azacitidine and/or its metabolites. Following intravenous and subcutaneous administration of ^{14}C-azacitidine, 85 and 50 % of the administered radioactivity was recovered in urine respectively, while < 1 % was recovered in faeces.

Pharmacokinetics in special populations

Hepatic impairment

The effects of hepatic impairment (see section 4.2), gender, age or race on the pharmacokinetics of azacitidine have not been formally studied.

Renal impairment

Renal impairment has no major effect on the pharmacokinetic exposure of azacitidine after single and multiple subcutaneous administrations.

Azacitidine can be administered to patients with renal impairment without initial dose adjustment provided these patients are monitored for toxicity since azacitidine and/or its metabolites are primarily excreted by the kidney.

5.3 Preclinical safety data

Azacitidine induces both gene mutations and chromosomal aberrations in bacterial and mammalian cell systems *in vitro*.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421).

Water for injection.

6.2 Incompatibilities

No further dilution with physiological solution is recommended. Hence, diluent compatibility studies are not applicable, see section 6.6 for more information on the reconstitution procedure.

6.3 Shelf life

Unopened powder vial

2 years.

After reconstitution

AZATURAS 25 mg/mL is compatible with the diluents and stable up to 1 hour at controlled room temperature (see section 6.4), when reconstituted as directed.
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 °C – 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.

The shelf life of the reconstituted medicinal product can be extended by reconstituting with refrigerated (2 °C to 8 °C) water for injections. When AZATURAS 25 mg/mL 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.

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.

6.4 Special precautions for storage

Store at or below 25 °C.
For storage conditions after reconstitution of the vial, see section 6.3.

6.5 Nature and contents of container

30 mL/20 mm flint moulded type-1 clear glass container, with a 20 mm dark grey chlorobutyl FluroTec-coated single slotted rubber stopper and a 20 mm aluminium flip-off seal.

One 30 mL vial is packed in a printed carton.

6.6 Special precautions for disposal and other handling

Recommendations for safe handling

AZATURAS 25 mg/mL is a cytotoxic medicine and caution should be exercised when handling and preparing AZATURAS 25 mg/mL suspensions. Procedures for proper handling and disposal of anticancer medicines should be applied.

If reconstituted AZATURAS 25 mg/mL 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 injection

AZATURAS 25 mg/mL 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 °C, 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 °C – 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.

Disposal

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pharma-Q Holdings (Pty) Ltd

50 Commando Road,

Industria West 2093

Johannesburg

South Africa

info@pharmaq.co.za

Tel: 011 247 1600

8. REGISTRATION NUMBERS

56/26/1140

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

29 July 2025

10. DATE OF REVISION OF THE TEXT

To follow