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**PROFESSSIONAL INFORMATION**

**SCHEDULING STATUS**

S4

## 1. NAME OF THE MEDICINE

INTAZA 150 (Powder for suspension for injection)

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 150 mg azacitidine.

Contains sugar: Each vial contains 150 mg mannitol.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Powder for suspension for injection

A white lyophilised powder or cake.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

INTAZA 150 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.


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### 4.2 Posology and method of administration

INTAZA 150 should be administered under the supervision of a doctor qualified in the use of cytotoxic medicines.

**Posology**

The recommended starting dose is 75 mg/m$^2$ subcutaneously, daily for seven days, every four weeks. Patients should be pre-medicated 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, a 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 a 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 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 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 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.


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| 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 |

*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 mEq/L occur, the dosage should be reduced by

50 % on the next course.

*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.

**Special populations**

*Patients with renal impairment*

No studies have been conducted in myelodysplastic syndrome (MDS) patients with decreased renal function. Since INTAZA 150 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 INTAZA 150 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*

INTAZA 150 and its metabolites are known to be substantially excreted by the kidney, and the risk of toxic reactions to INTAZA 150 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 INTAZA 150 in children and adolescents under 18 years of age has not been established.

**Method of administration**

Reconstituted INTAZA 150should 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 and dilution see section 6.6.

**4.3 Contraindications**

- Hypersensitivity to azacitidine or to any of the excipients in INTAZA 150 (see section 6.1)
- Patients with advanced malignant hepatic tumours
- Patients with severe renal impairment (creatinine clearance < 30 mLs/min)
- Pregnancy and lactation (see section 4.6)
- Children under the age of 18 years (see section 4.2)

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### 4.4 Special warnings and precautions for use

**Haematological toxicity**

Treatment with azacitidine 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 azacitidine treatment, especially in such patients with baseline serum albumin < 30 g/L. INTAZA 150 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 azacitidine in combination with other chemotherapeutic medicines 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 patients 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).

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Patients should be advised to report oliguria and anuria to the medical professional immediately.

Although 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 (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 section 4.8.

**Cardiac and pulmonary disease**

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. INTAZA 150 herapy 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 medicinal products 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), sulfotransferases (SULTs), and glutathione transferases (GSTs); interactions related to these metabolizing 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 drug interaction studies with azacitidine have been conducted.

### 4.6 Fertility, pregnancy and lactation

**Women of childbearing potential**

Women of child bearing age and men should use effective contraception during and up to 3 months after treatment.

**Pregnancy**

Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with INTAZA 150]. There is no adequate data on the use of INTAZA 150 in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.

INTAZA 150 should not be used during pregnancy (see section 4.3), if the patient becomes pregnant while taking INTAZA 150 the patient should be informed of the potential hazard to the foetus.

**Lactation**

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

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Because of the potential for tumorigenicity shown for INTAZA 150 in animal studies and the potential for serious adverse reactions, women treated with INTAZA 150 should not breastfeed (see section 4.3).

**Fertility**

Men should be advised not to father a child while receiving treatment with INTAZA 150

### 4.7 Effects on ability to drive and use machines

Since INTAZA 150 may cause blurred vision and less frequently somnolence and fatigue (see section 4.8), the ability to drive and operate machines may be negatively affected.

### 4.8 Undesirable effects

Table 1: Undesirable effects as per System Organ Class

| SYSTEM ORGAN CLASS | INCIDENCE | ADVERSE REACTION |
|---|---|---|
| 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 |
| | Unknown frequency | Necrotising fasciitis* |

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| | | |
|---|---|---|
| Blood and lymphatic system disorders | Frequent | Febrile neutropenia*, neutropenia, leukopenia, thrombocytopenia, anaemia, pancytopenia*, bone marrow failure |
| Immune system disorders | Less frequent | Hypersensitivity reactions |
| Metabolism and nutrition disorders | Frequent | Anorexia, decreased appetite, hypokalemia, 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, hypoesthesia |
| | Frequency unknown | Neurotoxicity |
| Eye disorders | Frequent | Eye haemorrhage, conjunctival haemorrhage |
| Cardiac disorders | Frequent | Pericardial effusion |
| | Less frequent | Pericarditis |
| Vascular disorders | Frequent | Hypotension*, hypertension, orthostatic hypotension, haematoma, flushing |
| Respiratory, thoracic and mediastinal disorders | Frequent | Dyspnoea, epistaxis, pleural effusion, dyspnoea exertional, pharyngolaryngeal pain, nasal congestion |

| | | |
|---|---|---|
| | Less frequent | interstitial lung disease |
| Gastro-intestinal disorders | Frequent | Diarrhoea, vomiting, constipation, nausea, abdominal pain (includes upper and abdominal discomfort), gastrointestinal haemorrhage* (includes mouth haemorrhage), haemorrhoidal haemorrhage, stomatitis, gingival bleeding, dyspepsia |
| | Less frequent | Peri-rectal abscess |
| Hepatobiliary disordes | Less frequent | Hepatic failure*, progressive hepatic coma |
| Skin and subcutaneous tissue disorders | Frequent | Petechiae, pruritus (includes generalized), rash, ecchymosis, purpura, alopecia, urticaria, erythema, rash macular, increased sweating |
| | 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 disorders | Frequent | Renal failure*, haematuria, elevated serum creatinine, dysuria |
| | Less frequent | Renal tubular acidosis |
| | Frequent | Pyrexia*, fatigue, asthenia, chest |

| | | |
|---|---|---|
| General disorders and administrative site conditions | | 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 |
| | Less frequent | injection site necrosis (at injection site) |
| Investigations | Frequent | Weight decreased, increased blood creatine |

*(* = rarely fatal cases have been reported)*

**Description of selected adverse reactions**

*Haematologic adverse reactions*

The most commonly 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 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*

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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 antiinfectives 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 non-steroidal anti-inflammatory drugs (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

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*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*

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).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked 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.

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### 4.9 Overdose

Symptoms of overdosage may include diarrhoea, nausea and vomiting.

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 INTAZA 150 overdosage.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, alkylating agents

A 26 – Cytostatic agents

ATC code: L01BC07

Azacitidine exerts its antineoplastic effects by causing hypomethylation of DNA and direct cytotoxicity on abnormal haematopoietic cells in the bone marrow by inhibition of DNA cytosine methyltransferase. 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

*Absorption*

A pharmacokinetic study of azacitidine was performed by administering a single 75 mg/m$^2$ subcutaneous (SC) and intravenous (IV) dose. Azacitidine was rapidly absorbed after a single 75 mg/m$^2$ SC dose. The peak plasma azacitidine concentration of 750 ± 403 ng/ml occurred in ½ hr. The bioavailability of SC azacitidine relative to the IV administered dose was approximately 89 % based on the AUC.

*Distribution*

Mean volume of distribution following IV administration was 76 ± 26 L. Mean apparent SC clearance was 167 ± 49 L/hr and mean half-life after SC administration was 41 ± 8 minutes.

*Biotransformation*

*In vitro* incubation of azacitidine 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 of1,0 µM to 100,0 µM does not induce CYP 1A2, 2C19 or 3A4/5.

*Elimination*

Azacitidine and its metabolites are primarily eliminated by urinary excretion. Following IV administration of radioactive azacitidine, 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 14C-azacitidine was 50 %. The mean elimination half-lives of total radioactivity (azacitidine and metabolites) were about 4 hours and were similar after IV and SC administrations.

**Special populations**

The effects of special populations, e.g. 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

Water for injection

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### 6.2 Incompatibilities

This medicinal product must not be mixed with other medicines except those mentioned in section 6.6.

### 6.3 Shelf life

*Unopened vials:*

3 years.

*After reconstitution:*

From a microbiological point of view, the medicine should be used immediately. If not used immediately, inuse storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 8 hours when stored between 2 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 °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.

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

Keep out of reach of children.

### 6.4 Special precautions for storage

Store at or below 25 °C.

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

### 6.5 Nature and contents of container

50 ml Type I clear moulded glass vial with 20 mm grey siliconised westar rubber stopper and 20 mm white aluminium flip off white seal or 20 mm white aluminum flip off white plain seal.

### 6.6 Special precautions for disposal and other handling

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*Recommendations for safe handling*

INTAZA 150 is a cytotoxic medicine and, as with other potentially toxic compounds, caution should be exercised when handling and preparing INTAZA 150 suspensions. Procedures for proper handling and disposal of cytotoxic medicines should be applied. If reconstituted INTAZA 150 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 administration*

INTAZA 150 should be reconstituted aseptically with 6 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 25 mg/ml azacitidine.

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

Doses greater than 6 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.

*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

Accord Healthcare (Pty) Limited

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**PROFESSSIONAL INFORMATION**

Building 2, Tuscany Office Park

6 Coombe Place

Rivonia

Johannesburg

South Africa

## 8. REGISTRATION NUMBER(S)

57/26/0490.489

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

15 July 2025

## 10. DATE OF REVISION OF THE TEXT

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