AMENDED PROPOSED PROFESSIONAL INFORMATION (CLEAN COPY)

SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

INTAZA 100 (lyophilised powder for suspension for injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg azacitidine.

Contains sugar: Each vial contains 100 mg mannitol

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Lyophilised powder for suspension for injection.

A white lyophilized powder or cake.

4. CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS:

INTAZA 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

INTAZA 100 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.

WBC or platelet nadir %	Bone marrow biopsy cellularity at time of nadir (%)

decrease in counts from baseline			
	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 MDS patients with decreased renal function. Since **INTAZA 100** 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 100** 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 100 and its metabolites are known to be substantially excreted by the kidney, and the risk of toxic

reactions to **INTAZA 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 **INTAZA 100** in children and adolescents under 18 years of age has not been established.

Method of administration

Reconstituted **INTAZA 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 where the site is tender, bruised, red, or hard.

For instructions on reconstitution and dilution see section 6.6.

4.3 CONTRA-INDICATIONS:

- **INTAZA 100** is contra-indicated in patients with a known hypersensitivity to azacitidine or to any of the ingredients of **INTAZA 100** (see section 2).
- 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).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

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

Treatment with **INTAZA 100** is associated with neutropenia and thrombocytopenia. Complete blood counts should be performed as needed to monitor administration of the recommended dosage for the first cycle, dosage for subsequent cycles should be reduced or delayed based on nadir counts and haematologic response (see

section 4.2).

Safety and effectiveness of **INTAZA 100** in patients with myelodysplastic syndrome (MDS) and hepatic or renal impairment have not been studied.

Because **INTAZA 100** is potentially hepatotoxic in patients with severe, pre-existing hepatic impairment, caution is needed in patients with liver disease. Patients with extensive tumour burden due to metastatic disease have been reported to experience progressive hepatic coma and death during **INTAZA 100** treatment, especially in such patients with baseline albumin < 30 g/L. **INTAZA 100** is contra-indicated in patients with advanced malignant hepatic tumours.

Renal abnormalities ranging from elevated serum creatinine to renal failure and death were reported in patients treated with intravenous azacitidine, as found in **INTAZA 100,** in combination with other chemotherapeutic agents for non-MDS conditions. In addition, renal tubular acidosis, defined as a fall in serum bicarbonate to < 20 mEq/L in association with an alkaline urine and hypokalaemia (serum potassium< 3 mEq/L) were reported in patients with Chronic myeloid leukaemia (CML) treated with azacitidine as found in **INTAZA 100** and etoposide. If unexplained elevations of serum creatinine or BUN or reductions in serum bicarbonate (< 20 mEq/L) occur, the dosage should be reduced or held (see section 4.2).
Patients with renal impairment should be closely monitored for toxicity since **INTAZA 100** and its metabolites are primarily excreted by the kidney.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTION

Interaction studies with **INTAZA 100** 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 **INTAZA 100** metabolism may be affected by known microsomal enzyme inhibitors or inducers has not been studied. *In vitro* studies of **INTAZA 100** with human cultured hepatocytes indicate that **INTAZA 100** at concentrations of 1,0 µM to 100 µM does not induce CYP1A2, 2C19, or 3A4/5. The potential of **INTAZA 100** to inhibit cytochrome P450 (CYP) enzymes is not known.

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 100**. There is no adequate data on the use of **INTAZA 100** in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown.

INTAZA 100 should not be used during pregnancy, if the patient becomes pregnant while taking **INTAZA 100**, 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. Because of the potential for tumorigenicity shown for **INTAZA 100** in animal studies and the potential for serious adverse reactions, women treated with **INTAZA 100** should not breastfeed.

Fertility

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

4.7 Effects on ability to drive and use machines:

Since **INTAZA 100** may cause blurred vision and less frequently somnolence and fatigue (see section 4.8), the ability to drive and use machines may be negatively affected.

4.8 UNDESIRABLE EFFECTS

The following side effects may occur with **INTAZA 100**.

Infections and infestations

Frequent: Nasopharyngitis, pneumonia, upper respiratory tract infection, bacterial infection

Blood and the lymphatic system disorders

Frequent: Anaemia, febrile neutropenia, leukopenia, neutropenia, thrombocytopenia, lymphadenopathy

Less frequent: Agranulocytosis

Immune system disorders

Frequent: Hypersensitivity

Metabolism and nutrition disorders

Frequent: Anorexia, hypokalaemia

Psychiatric disorders

Frequent: Anxiety, insomnia

Nervous system disorders

Frequent: Dizziness, burning sensation, hypoesthesia, intra-cranial haemorrhage

Frequency unknown: Neurotoxicity

Vascular disorders

Frequent: Petechiae, flushing, haematoma

Frequency unknown: Blood complications

Respiratory, thoracic and mediastinal disorders

Frequent: Dyspnoea, pharyngitis, haemoptysis, nasal congestion

Gastrointestinal disorders

Frequent: Constipation, diarrhoea, nausea, vomiting, gastrointestinal haemorrhage, gingival bleeding, loose stools, oral mucosal petechiae, stomatitis, tongue ulceration

Less frequent: Perirectal abscess

Hepato-biliary disorders

Frequency unknown: Hepatic dysfunction

Skin and subcutaneous tissue disorders

Frequent: Ecchymosis, erythema, increased sweating, rash, pruritic rash, urticaria

Musculoskeletal and connective tissue disorders

Frequent: Arthralgia, myalgia

Renal and urinary disorders

Frequent: Dysuria

Frequency unknown: Renal dysfunction

General disorders and administration site conditions

Frequent: Chest pain, fatigue, aggravated injection site bruising, injection site erythema, injection site pain, injection site reaction, malaise, rigors, injection site granuloma, injection site pigmentation changes, injection site swelling, lethargy

Investigations

Frequent: Increased blood creatine

Injury, poisoning and procedural complications

Frequent: Post procedural haemorrhage

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 "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za

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 100** overdosage.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 26 – Cytostatic agents

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 of 1,0 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 ^{14}C-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

6.2 Incompatibilities

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

6.3 Shelf-life

24 months

After reconstitution:

From a microbiological point of view, the medicine should be used immediately. If not used immediately, in-use 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.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep out of reach of children.

For storage conditions after reconstitution and dilution of the medicine, see section 6.3.

6.5 Nature and contents of the container

A 30 ml, clear, type 1 glass vial, sealed with a grey bromo-butyl, siliconised rubber stopper and white aluminium flip-off seal.

6.6 Special precautions for disposal and other handling

Recommendations for safe handling:

INTAZA 100 is a cytotoxic medicine and, as with other potentially toxic compounds, caution should be exercised when handling and preparing **INTAZA 100** suspensions. Procedures for proper handling and disposal of cytotoxic medicines should be applied.

If reconstituted **INTAZA 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:

INTAZA 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 25 mg/ml azacitidine.

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.

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) Ltd.

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8. REGISTRATION NUMBER

INTAZA 100: 51/26/0453.452

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

17 November 2020

10. DATE OF REVISION OF THE TEXT

23 July 2021