# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. Name of the medicinal product
Azacitidine for Injection 100 mg/vial**.**

## 2.Description /Label claim
Each vial contains Azacitidine 100 mg.

For the full list of excipients, see section 6.1

## 3. Pharmaceutical form
**Description**
Lyophilized powder for Injection.
White Lyophilized cake or powder in 30 mL type I with 20 mm moulded flint glass vial with 20 mm igloo design grey rubber stopper and sealed with aluminium seal having polypropylene disc.

## 4. Clinical particulars

### 4.1 Therapeutic indications
### 4.1.1 Myelodysplastic Syndromes (MDS)
Azacitidine is indicated for treatment of patients with the following French-American-British (FAB) myelodysplastic syndrome subtypes: refractory anemia (RA) or refractory anemia with ringed side roblasts (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMMoL).

### 4.2 Posology and Method of administration
Posology

### 4.2.1 First Treatment Cycle
The recommended starting dose for the first treatment cycle, for all patients regardless of baseline hematology laboratory values, is 75 mg/m$^2$ subcutaneously or intravenously, daily for 7 days. Premedicate patients for nausea and vomiting. Obtain complete blood counts, liver chemistries and serum creatinine prior to the first dose.

### 4.2.2 Subsequent Treatment Cycles
Repeat cycles every 4 weeks. The dose may be increased to 100 mg/m$^2$ if no beneficial effect is seen after 2 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 to 6 cycles. However, complete or partial response may require additional treatment cycles. Treatment may be continued as long as the patient continues to benefit. Monitor patients for hematologic response and renal toxicities [see Warnings and Precautions (4.4)], and delay or reduce dosage if necessary as described below.

### 4.2.3 Dosage Adjustment Based on Hematology Laboratory Values

- For patients with baseline (start of treatment) WBC greater than or equal to 3.0 x10 $^{9}$ /L, ANC greater than or equal to 1.5 x$10^{9}$ /L, and platelets greater than or equal to 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( x $10^{9}$/L) | Platelets (x $10^{9}$/L) | |
| Less than 0.5 | Less than 25 | 50% |
| 0.5-1.5 | 25-50 | 67% |
| Greater than 1.5 | Greater than 50 | 100% |

- For patients whose baseline counts are WBC less than 3.0 x$10^{9}$ /L, ANC less than 1.5 x$10^{9}$ /L, or platelets less than 75.0 x$10^{9}$ /L, base dose adjustments 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 continue the current dose.

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

If a nadir as defined in the table above has occurred, give the next course 28 days after the start of the preceding course, provided that both the WBC and the platelet counts are greater than 25% above the nadir and rising. If a greater than 25% increase above the nadir is not seen by day 28, reassess counts every 7 days. If a 25% increase is not seen by day 42, reduce the scheduled dose by 50%.

### 4.2.4 Dosage Adjustment Based on Serum Electrolytes and Renal Toxicity

If unexplained reductions in serum bicarbonate levels to less than 20 mEq/L occur, reduce the dosage by 50% for the next course. Similarly, if unexplained elevations of BUN or serum creatinine occur, delay the next cycle until values return to normal or baseline and reduce the dose by 50% for the next course [see Warnings and Precautions (4.4)].

**4.2.5 Use in Geriatric Patients**

Azacitidine and its metabolites are known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, select the dose carefully and monitor renal function [see Warnings and Precautions (4.4) and Use in Specific Populations (4.6.5)].

Azacitidine is a cytotoxic drug. Follow applicable special handling and disposal procedures. The Azacitidine vial is single-dose and does not contain any preservatives. Discard unused portions of each vial properly [see How Supplied/Storage and Handling (6.5)]. Do not save any unused portions for later administration.

**Instructions for Subcutaneous Administration**

Reconstitute Azacitidine aseptically with 4 mL sterile water for injection. Inject the diluent 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. Do not filter the suspension after reconstitution. Doing so could remove the active substance.

**Preparation for Immediate Subcutaneous Administration:**

For doses requiring more than 1 vial, divide the dose equally between the syringes (e.g., dose 150 mg = 6 mL, 2 syringes with 3 mL in each syringe) and inject into two separate sites. Due to retention in the vial and needle, it may not be feasible to withdraw all of the suspension from the vial. The product may be held at room temperature for up to 1 hour, but must be administered within 1 hour after reconstitution.

**Preparation for Delayed Subcutaneous Administration:**

The reconstituted product may be kept in the vial or drawn into a syringe. For doses requiring more than 1 vial, divide the dose equally between the syringes (e.g., dose 150 mg = 6 mL, 2 syringes with 3 mL in each syringe) and inject into two separate sites. Due to retention in the vial and needle, it may not be feasible to withdraw all of the suspension from the vial. The product must be refrigerated immediately. When Azacitidine is reconstituted using water for injection that has not been refrigerated, the reconstituted product may be held under refrigerated conditions (2ºC - 8ºC, 36ºF - 46ºF) for up to 8 hours. When Azacitidine is reconstituted using refrigerated (2ºC - 8ºC, 36ºF - 46ºF) water for injection, the reconstituted product may be stored under refrigerated conditions (2ºC - 8ºC, 36ºF - 46ºF) for up to 22 hours. After removal from refrigerated conditions, the suspension may be allowed to equilibrate to room temperature for up to 30 minutes prior to administration.

**Subcutaneous Administration**

To provide a homogeneous suspension, the contents of the dosing syringe must be re-suspended immediately prior to administration. To re-suspend, vigorously roll the syringe between the palms until a uniform, cloudy suspension is achieved.
Azacitidine suspension is administered subcutaneously. Rotate sites for each 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.

**Instructions for Intravenous Administration**
Reconstitute the appropriate number of Azacitidine vials to achieve the desired dose. Reconstitute each vial with 10 mL sterile water for injection. Vigorously shake or roll the vial until all solids are dissolved. The resulting solution will contain azacitidine 10 mg/mL. The solution should be clear. Parenteral drug product should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
Withdraw the required amount of Azacitidine solution to deliver the desired dose and inject into a 50 -100 mL infusion bag of either 0.9% Sodium Chloride Injection or Lactated Ringer's Injection.

**Intravenous Solution Incompatibility**
Azacitidine is incompatible with 5% Dextrose solutions, Hespan, or solutions that contain bicarbonate. These solutions have the potential to increase the rate of degradation of Azacitidine and should therefore be avoided.

**Intravenous Administration**
Azacitidine solution is administered intravenously. Administer the total dose over a period of 10 – 40 minutes. The administration must be completed within 1 hour of reconstitution of the Azacitidine vial.

**4.3 Contraindications**
**Advanced Malignant Hepatic Tumors**
Azacitidine is contraindicated in patients with advanced malignant hepatic tumors [see Warnings and Precautions (4.4)].

**Hypersensitivity to Azacitidine or Mannitol**
Azacitidine is contraindicated in patients with a known hypersensitivity to azacitidine or mannitol.

**4.4 Special warnings and precautions for use**
**4.4.1 Anemia, Neutropenia and Thrombocytopenia**
Azacitidine causes anemia, neutropenia and thrombocytopenia. Monitor complete blood counts frequently for response and/or toxicity, at a minimum, prior to each dosing cycle. After administration of the recommended dosage for the first cycle, adjust dosage for subsequent cycles based on nadir counts and hematologic response [see Dosage and Administration (4.2.3)].

**4.4.2 Hepatotoxicity in Patients with Severe Pre-existing Hepatic Impairment**

Because azacitidine is potentially hepatotoxic in patients with severe pre-existing hepatic impairment, caution is needed in patients with liver disease. Patients with extensive tumor burden due to metastatic disease have been reported to experience progressive hepatic coma and death during azacitidine treatment, especially in such patients with baseline albumin <30 g/L. Azacitidine is contraindicated in patients with advanced malignant hepatic tumors [see Contraindications (4.4.1)]. Monitor liver chemistries prior to initiation of therapy and with each cycle.

Safety and effectiveness of Azacitidine in patients with MDS and hepatic impairment have not been studied as these patients were excluded from the clinical trials.

**4.4.3 Renal Toxicity**

Renal toxicity ranging from elevated serum creatinine to renal failure and death have been reported in patients treated with intravenous azacitidine in combination with other chemotherapeutic agents for nonMDS conditions. In addition, renal tubular acidosis, defined as a fall in serum bicarbonate to <20 mEq/L in association with an alkaline urine and hypokalemia (serum potassium <3 mEq/L) developed in 5 patients with CML treated with azacitidine and etoposide. Monitor serum creatinine and electrolytes prior to initiation of therapy and with each cycle. If unexplained reductions in serum bicarbonate <20 mEq/L or elevations of BUN or serum creatinine occur, reduce or hold the dose [see Dosage and Administration (2.4)].

toxicity [see Dosage and Administration (4.2.4, 4.2.5)]. Patients with MDS and renal impairment were excluded from the clinical studies.

**4.4.4 Tumor Lysis Syndrome**

Azacitidine may cause fatal or serious tumor lysis syndrome, including in patients with MDS. Tumor lysis syndrome may occur despite concomitant use of allopurinol. Assess baseline risk and monitor and treat as appropriate.

**4.4.5 Embryo-Fetal Risk**

Based on the mechanism of action and findings in animals, Azacitidine can cause fetal harm when administered to a pregnant woman. Azacitidine administered to pregnant rats via a single intraperitoneal (IP) dose approximating 8% of the recommended human daily dose caused fetal death and anomalies [see Use in Specific Populations (4.6.1)].

Advise females with reproductive potential to avoid pregnancy during treatment with Azacitidine [see Use in Specific Populations (4.6.3)]. Men should be advised to not father a child while receiving treatment with Azacitidine.

**4.5 Interaction with other medicinal products and other forms of interaction**

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

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

An *in vitro* study with cultured human hepatocytes indicated that azacitidine at concentrations up to 100 µM (IV Cmax = 10.6 µM) does not cause any inhibition of CYP2B6 and CYP2C8.
The potential of azacitidine to inhibit other cytochrome P450 (CYP) enzymes is not known. In vitro studies 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.

**4.6 Fertility, pregnancy and lactation**

**4.6.1Pregnancy**

Risk Summary

Based on its mechanism of action and findings in animals, Azacitidine can cause fetal harm when administered to a pregnant woman [see Clinical Pharmacology (5.1.1)]. There are no data on the use of azacitidine in pregnant women. Azacitidine was teratogenic and caused embryo-fetal lethality in animals at doses lower than the recommended human daily dose (see Data). Advise pregnant women of the potential risk to the fetus.
The background rate of major birth defects and miscarriage is unknown for the indicated population. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. General population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Data

*Animal Data*

Early embryotoxicity studies in mice revealed a 44% frequency of intrauterine embryonal death (increased resorption) after a single IP (intraperitoneal) injection of 6 mg/m$^2$ (approximately 8% of the recommended human daily dose on a mg/m basis) azacitidine on gestation day 10. Developmental abnormalities in the brain have been detected in mice given azacitidine on or before gestation day 15 at doses of ~3-12 mg/m$^2$ (approximately 4%-16% the recommended human daily dose on a mg/m$^2$ basis).
In rats, azacitidine was clearly embryotoxic when given IP on gestation days 4-8 (postimplantation) at a dose of 6 mg/m$^2$ (approximately 8% of the recommended human daily on a mg/m$^2$ basis) given on gestation day 9, 10, 11 or 12. In this study azacitidine caused fetal death when administered at 3-12 mg/m$^2$ on gestation days 9 and 10; average live animals per litter was reduced to 9% of control at the highest dose on gestation day 9. Fetal anomalies included: CNS anomalies (exencephaly/encephalocele), limb anomalies (micromelia, club foot, syndactyly, oligodactyly), and others (micrognathia, gastroschisis, edema, and rib abnormalities).

**4.6.2 Lactation**

*Risk Summary*

There is no information regarding the presence of azacitidine in human milk, the effects of Azacitidine on the breastfed infant, or the effects of Azacitidine on milk production. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for azacitidine in animal studies [see Nonclinical Toxicology (5.3.1)] and the potential for serious

adverse reactions in nursing infants from Azacitidine, advise patients not to breastfeed during treatment with Azacitidine.

**4.6.3 Females and Males of Reproductive Potential**

Based on its mechanism of action and findings in animals, Azacitidine can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (4.6.1)].

*Pregnancy Testing*

Verify the pregnancy status of females of reproductive potential prior to initiating Azacitidine.

**Contraception**

Females

Advise females of reproductive potential to avoid pregnancy during treatment with Azacitidine.

Males

Males with female sexual partners of reproductive potential should not father a child and should use effective contraception during treatment with Azacitidine

*Infertility*

Based on animal data, azacitidine could have an effect on male or female fertility [se Nonclinical Toxicology (5.3.1)].

**4.6.4 Pediatric Use**

Safety and effectiveness in pediatric patients have not been established.

**4.6.5 Geriatric Use**

Of the total number of patients in Studies 1, 2 and 3, 62% were 65 years and older and 21% were 75 years and older. No overall differences in effectiveness were observed between these patients and younger patients. In addition, there were no relevant differences in the frequency of adverse reactions observed in patients 65 years and older compared to younger patients.

Of the 179 patients randomized to azacitidine in Study 4, 68% were 65 years and older and 21% were 75 years and older. Survival data for patients 65 years and older were consistent with overall survival results. The majority of adverse reactions occurred at similar frequencies in patients <65 years of age and patients 65 years of age and older. Elderly patients are more likely to have decreased renal function. Monitor renal function in these patients *[see Dosage and Administration (4.2.5) and Warnings and Precautions (4.4)]*.

**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. Therefore, caution is recommended when driving or operating machines.

**4.8 Undesirable effects**

The following adverse reactions are described in other labeling sections:

- Anemia, Neutropenia and Thrombocytopenia [see Warnings and Precautions (4.4.1)]
- Hepatotoxicity in Patients with Severe Pre-existing Hepatic Impairment [see Warnings

and Precautions (4.4.2)]
- Renal Toxicity [see Warnings and Precautions (4.4.3)]

- Tumor Lysis Syndrome [see Warnings and Precautions (4.4.4)]
- Embryo-Fetal Risk [see Warnings and Precautions (4.4.5)]

**Most Commonly Occurring Adverse Reactions (Subcutaneous or Intravenous Route):** nausea, anemia, thrombocytopenia, vomiting, pyrexia, leukopenia, diarrhea, injection site erythema, constipation, neutropenia, ecchymosis. The most common adverse reactions by intravenous route also included petechiae, rigors, weakness and hypokalemia.
Adverse Reactions Most Frequently (>2%) Resulting in Clinical Intervention (Subcutaneous or Intravenous Route):
Discontinuation: leukopenia, thrombocytopenia, neutropenia.
Dose Held: leukopenia, neutropenia, thrombocytopenia, pyrexia, pneumonia, febrile neutropenia.
Dose Reduced: leukopenia, neutropenia, thrombocytopenia.

**4.8.1 Adverse Reactions in Clinical Trials**
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.
The data described below reflect exposure to Azacitidine in 443 MDS patients from 4 clinical studies. Study 1 was a supportive-care controlled trial (subcutaneous administration), Studies 2 and 3 were single arm studies (one with subcutaneous administration and one with intravenous administration), and Study 4 was an international randomized trial (subcutaneous administration) [see Clinical Studies (14)]. In Studies 1, 2 and 3, a total of 268 patients were exposed to Azacitidine, including 116 exposed for 6 cycles (approximately 6 months) or more and 60 exposed for greater than 12 cycles (approximately one year). Azacitidine was studied primarily in supportive-care controlled and uncontrolled trials (n=150 and n=118, respectively). The population in the subcutaneous studies (n=220) was 23 to 92 years old (mean 66.4 years), 68% male, and 94% white, and had MDS or AML. The population in the intravenous study (n=48) was 35 to 81 years old (mean 63.1 years), 65% male, and 100% white. Most patients received average daily doses between 50 and 100 $mg/m^2$.
In Study 4, a total of 175 patients with higher-risk MDS (primarily RAEB and RAEB-T subtypes) were exposed to Azacitidine. Of these patients, 119 were exposed for 6 or more cycles, and 63 for at least 12 cycles. The mean age of this population was 68.1 years (ranging from 42 to 83 years), 74% were male, and 99% were white. Most patients received daily Azacitidine doses of 75 $mg/m^2$.
Table 1 presents adverse reactions occurring in at least 5% of patients treated with Azacitidine (subcutaneous) in Studies 1 and 2. It is important to note that duration of exposure was longer for the Azacitidine-treated group than for the observation group: patients received Azacitidine for a mean of 11.4 months while mean time in the observation arm was 6.1 months.

| **Table 1: Most Frequently Observed Adverse Reactions (≥ 5.0% in All Subcutaneous Azacitidine Treated Patients; Studies 1 and 2)** | | |
|---|---|---|
| | **Number (%) of Patients** | |
| **System Organ Class Preferred Term[a]** | **All Azacitidine[b] (N=220)** | **Observation[c] (N=92)** |
| **Blood and lymphatic system disorders** | | |
| Anemia | 153(70) | 59(64) |
| Anemia aggravated | 12(6) | 5(5) |
| Febrile neutropenia | 36(16) | 4(4) |
| Leukopenia | 106(48) | 27(29) |
| Neutropenia | 71(32) | 10(11) |
| Thrombocytopenia | 144(66) | 42(46) |
| **Gastrointestinal disorders** | | |
| Abdominal tenderness | 26(12) | 1(1) |
| Constipation | 74(34) | 6(7) |
| Diarrhea | 80(36) | 13(14) |
| Gingival bleeding | 21(10) | 4(4) |
| Loose stools | 12(6) | 0 |
| Mouth hemorrhage | 11(5) | 1(1) |
| Nausea | 155(71) | 16(17) |
| Stomatitis | 17(8) | 0 |
| Vomiting | 119(54) | 5(5) |
| **General disorders and administration site conditions** | | |

| | | |
|---|---|---|
| Chest pain | 36(160 | 5(5) |
| Injection site bruising | 31(14) | 0 |
| Injection site erythema | 77(35) | 0 |
| Injection site granuloma | 11(5) | 0 |
| Injection site pain | 50(23) | 0 |
| Injection site pigmentation changes | 11(5) | 0 |
| Injection site pruritus | 15(7) | 0 |
| Injection site reaction | 30(14) | 0 |
| Injection site swelling | 11(5) | 0 |
| Lethargy | 17(8) | 2(2) |
| Malaise | 24(11) | 1(1) |
| Pyrexia | 114(52) | 28(30) |
| **Infections and infestations** | | |
| Nasopharyngitis | 32(15) | 3(3) |
| Pneumonia | 24(11) | 5(5) |
| Upper respiratory tract infection | 28(13) | 4(4) |
| **Injury, poisoning, and procedural complications** | | |
| Post procedural hemorrhage | 13(6) | 1(1) |
| **Metabolism and nutrition disorders** | | |
| Anorexia | 45(21) | 6(7) |
| **Musculoskeletal and connective tissue disorders** | | |

| | | |
|---|---|---|
| Arthralgia | 49(22) | 3(3) |
| Chest wall pain | 11(5) | 0 |
| Myalgia | 35(16) | 2(2) |
| **Nervous system disorders** | | |
| Dizziness | 41(19) | 5(5) |
| Headache | 48(22) | 10(11) |
| **Psychiatric disorders** | | |
| Anxiety | 29(13) | 3(3) |
| Insomnia | 24(11) | 4(4) |
| **Respiratory, thoracic and mediastinal disorders** | | |
| Dyspnea | 64(29) | 11(12) |
| **Skin and subcutaneous tissue disorders** | | |
| Dry skin | 11(5) | 1(1) |
| Ecchymosis | 67(31) | 14(15) |
| Erythema | 37(17) | 4(4) |
| Rash | 31(14) | 9(10) |
| Skin nodule | 11(5) | 1(1) |
| Urticaria | 13(6) | 1(1) |
| **Vascular disorders** | | |
| Hematoma | 19(9) | 0 |
| Hypotension | 15(7) | 2(2) |
| Petechiae | 52(24) | 8(9) |

[a]Multiple terms of the same preferred terms for a patient are only counted once within each treatment group.

[b]Includes adverse reactions from all patients exposed to Azacitidine, including patients after crossing over from observations.

[c]Includes adverse reactions from observation period only; excludes any adverse events after crossover to Azacitidine

Table 2 presents adverse reactions occurring in at least 5% of patients treated with Azacitidine in Study 4.
Similar to Studies 1 and 2 described above, duration of exposure to treatment with Azacitidine was longer (mean 12.2 months) compared with best supportive care (mean 7.5 months).

**Table 2: Most Frequently Observed Adverse Reactions (≥ 5.0% in Azacitidine Treated Patients and the Percentage with NCI CTC Grade 3/4 Reactions;Study 4)**

| | **Number (%) of Patients** | | | |
|---|---|---|---|---|
| | **Any Grade** | | **Grade 3/4** | |
| **System Organ Class Preferred Term[a]** | **Azacitidine (N=102)** | **Best Supportive Care Only (N=102)** | **Azacitidine (N=175)** | **Best Supportive Care Only (N=102)** |
| **Blood and lymphatic system disorders** | | | | |
| Anemia | 90(51) | 45(44) | 24(14) | 9(9) |
| Febrile neutropenia | 24(14) | 10(10) | 22(13) | 7(7) |
| Leukopenia | 32(18) | 2(2) | 26(15) | 1(1) |
| Neutropenia | 115(66) | 29(28) | 107(61) | 22(22) |
| Thrombocytopenia | 122(70) | 35(34) | 102(58) | 29(28) |
| **Gastrointestinal disorders** | | | | |

| | | | | |
|---|---|---|---|---|
| Abdominal pain | 22(13) | 7(7) | 7(4) | 0 |
| Constipation | 88(50) | 8(8) | 2(1) | 0 |
| Dyspepsia | 10(6) | 2(2) | 0 | 0 |
| Nausea | 84(48) | 12(12) | 3(2) | 0 |
| Vomiting | 47(27) | 7(7) | 0 | 0 |
| **General disorders and administration site conditions** | | | | |
| Fatigue | 42(24) | 12(12) | 6(3) | 2(2) |
| Injection site bruising | 9(5) | 0 | 0 | 0 |
| Injection site erythema | 75(43) | 0 | 0 | 0 |
| Injection site hematoma | 11(6) | 0 | 0 | 0 |
| Injection site induration | 9(5) | 0 | 0 | 0 |
| Injection site pain | 33(19) | 0 | 0 | 0 |
| Injection site rash | 10(6) | 0 | 0 | 0 |
| Injection site reaction | 51(29) | 0 | 1(1) | 0 |
| Pyrexia | 53(30) | 18(18) | 8(5) | 1(1) |
| **Infections and infestations** | | | | |
| Rhinitis | 10(6) | 1(1) | 0 | 0 |
| Upper respiratory tract infection | 16(9) | 4(4) | 3(2) | 0 |
| Urinary tract infection | 15(9) | 3(3) | 3(2) | 0 |
| **Investigations** | | | | |
| Weight decreased | 14(8) | 0 | 1(1) | 0 |

| | | | | |
|---|---|---|---|---|
| **Metabolism and nutrition disorders** | | | | |
| Hypokalemia | 11(6) | 3(3) | 3(2) | 3(3) |
| **Nervous system disorders** | | | | |
| Lethargy | 13(7) | 2(2) | 0 | 1(1) |
| **Psychiatric disorders** | | | | |
| Anxiety | 9(5) | 1(1) | 0 | 0 |
| Insomnia | 15(9) | 3(3) | 0 | 0 |
| **Renal and urinary disorders** | | | | |
| Hematuria | 11(6) | 2(2) | 4(2) | 1(1) |
| **Respiratory, thoracic and mediastinal disorders** | | | | |
| Dyspnea | 26(15) | 5(5) | 6(3) | 2(2) |
| Dyspnea exertional | 9(5) | 1(1) | 0 | 0 |
| Pharyngolaryngeal pain | 11(6) | 3(3) | 0 | 0 |
| **Skin and subcutaneous tissue disorders** | | | | |
| Erythema | 13(7) | 3(3) | 0 | 0 |
| Petechiae | 20(11) | 4(4) | 2(1) | 0 |
| Pruritus | 21(12) | 2(2) | 0 | 0 |
| Rash | 18(10) | 1(1) | 0 | 0 |
| **Vascular disorders** | | | | |
| Hypertension | 15(9) | 4(4) | 2(1) | 2(2) |

[a]Multiple terms of the same preferred term from a patient were only counted once within each treatment group.

In Studies 1, 2 and 4 with subcutaneous administration of Azacitidine, adverse reactions of neutropenia, thrombocytopenia, anemia, nausea, vomiting, diarrhea, constipation, and injection site erythema/reaction tended to increase in incidence with higher doses of Azacitidine. Adverse reactions that tended to be more pronounced during the first 1 to 2 cycles of subcutaneous treatment compared with later cycles included thrombocytopenia, neutropenia, anemia, nausea, vomiting, injection site erythema/pain/bruising/reaction, constipation, petechiae, dizziness, anxiety, hypokalemia, and insomnia. There did not appear to be any adverse reactions that increased in frequency over the course of treatment.

Overall, adverse reactions were qualitatively similar between the intravenous and subcutaneous studies. Adverse reactions that appeared to be specifically associated with the intravenous route of administration included infusion site reactions (e.g. erythema or pain) and catheter site reactions (e.g. infection, erythema, or hemorrhage).

In clinical studies of either subcutaneous or intravenous Azacitidine, the following serious adverse reactions occurring at a rate of <5% (and not described in Tables 1 or 2) were reported:

**Blood and lymphatic system disorders:** agranulocytosis, bone marrow failure, pancytopenia splenomegaly.

**Cardiac disorders:** atrial fibrillation, cardiac failure, cardiac failure congestive, cardio-respiratory arrest, congestive cardiomyopathy.

**Eye disorders:** eye hemorrhage

**Gastrointestinal disorders:** diverticulitis, gastrointestinal hemorrhage, melena, perirectal abscess.

**General disorders and administration site conditions:** catheter site hemorrhage, general physical health deterioration, systemic inflammatory response syndrome.

**Hepatobiliary disorders:** cholecystitis.

**Immune system disorders:** anaphylactic shock, hypersensitivity.

**Infections and infestations:** abscess limb, bacterial infection, cellulitis, blastomycosis, injection site infection, Klebsiella sepsis, neutropenic sepsis, pharyngitis streptococcal, pneumonia

Klebsiella, sepsis, septic shock, Staphylococcal bacteremia, Staphylococcal infection, toxoplasmosis.

**Metabolism and nutrition disorders:** dehydration.

**Musculoskeletal and connective tissue disorders:** bone pain aggravated, muscle weakness, neck pain.

**Neoplasms benign, malignant and unspecified:** leukemia cutis.

**Nervous system disorders:** cerebral hemorrhage, convulsions, intracranial hemorrhage.

**Renal and urinary disorders:** loin pain, renal failure.

**Respiratory, thoracic and mediastinal disorders:** hemoptysis, lung infiltration, pneumonitis, respiratory distress.

**Skin and subcutaneous tissue disorders:** pyoderma gangrenosum, rash pruritic, skin induration.

**Surgical and medical procedures:** cholecystectomy.

**Vascular disorders:** orthostatic hypotension.

**Reporting of suspected adverse reactions:**
Reporting suspected adverse reactions after authorization of the medicinal product is important as it allows continued monitoring of the benefit–risk balance of the medicinal product. Healthcare professionals are requested to report any suspected adverse reactions to the marketing authorization holder or, where applicable, via the national reporting system https://pv.pharmacyboardkenya.org/

### 4.9 Overdose
One case of overdose with Azacitidine was reported during clinical trials. A patient experienced diarrhea, nausea, and vomiting after receiving a single intravenous dose of approximately 290 mg/m2, almost 4 times the recommended starting dose. The event resolved without sequelae, and the correct dose was resumed the following day. In the event of overdose, the patient should be monitored with appropriate blood counts and should receive supportive treatment, as necessary. There is no known specific antidote for Azacitidine overdose.

## 5. Pharmacological properties

### 5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antineoplastic agents, pyrimidine analogues; ATC code: L01BC07

**5.1.1 Mechanism of action**

Azacitidine is a pyrimidine nucleoside analog of cytidine. Azacitidine is believed to exert its antineoplastic effects by causing hypomethylation of DNA and direct cytotoxicity on abnormal hematopoietic 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 6 MDS patients following a single 75 $mg/m^2$ subcutaneous dose and a single 75 $mg/m^2$ intravenous dose.

**Absorption**

Azacitidine is rapidly absorbed after subcutaneous administration; the peak plasma azacitidine concentration of 750 ± 403 ng/ml occurred in 0.5 hour.

**Distribution**

The bioavailability of subcutaneous azacitidine relative to intravenous azacitidine is approximately 89%, based on area under the curve. Mean volume of distribution following intravenous dosing is 76 ± 26 L. Mean apparent subcutaneous clearance is 167 ± 49 L/hour and mean half-life after subcutaneous administration is 41 ± 8 minutes. The AUC and $C_{max}$ of subcutaneous administration of azacitidine in 21 patients with cancer were approximately dose proportional within the 25 to 100 $mg/m^2$ dose range. Multiple dosing at the recommended dose-regimen does not result in drug accumulation.

**Elimination**

Published studies indicate that urinary excretion is the primary route of elimination of azacitidine and its metabolites. Following intravenous administration of radioactive azacitidine to 5 cancer patients, the cumulative urinary excretion was 85% of the radioactive dose. Fecal excretion urine following subcutaneous administration of $^{14}C$-azacitidine was 50%. The mean elimination
half-lives of total radioactivity (azacitidine and its metabolites) were similar after intravenous and subcutaneous administrations, about 4 hours.

**Specific populations**

In patients with cancer the pharmacokinetics of azacitidine in 6 patients with normal renal function (Clcr >80 mL/min) and 6 patients with severe renal impairment (CLcr <30 mL/min) were compared following daily subcutaneous dosing (Days 1 through 5) at 75 $mg/m^2$ /day. Severe renal impairment increased azacitidine exposure by approximately 70% after single and 41% after multiple subcutaneous administrations. This increase in exposure was not correlated with an increase in adverse events. The exposure was similar to exposure in patients with normal renal function receiving 100 $mg/m^2$. Therefore, a Cycle 1 dose modification is not recommended. The effects of hepatic impairment, gender, age, or race on the pharmacokinetics of azacitidine have not been studied.

**5.3 Preclinical safety data**

**5.3.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**

The potential carcinogenicity of azacitidine was evaluated in mice and rats. Azacitidine induced tumors of the hematopoietic system in female mice at 2.2 mg/kg (6.6 mg/$m^2$ , approximately 8% the recommended human daily dose on a mg/m basis) administered IP three times per week for 52 weeks. An increased incidence of tumors in the lymphoreticular system, lung, mammary gland, and skin was seen in mice treated with azacitidine IP at 2.0 mg/kg (6.0 mg/$m^2$ , approximately 8% the recommended human daily dose on a mg/$m^2$ basis) once a week for 50 weeks. A tumorigenicity study in rats dosed twice weekly at 15 or 60 mg/$m^2$ (approximately 20%-80% the recommended human daily dose on a mg/$m^2$ basis) revealed an increased incidence of testicular tumors compared with controls.

The mutagenic and clastogenic potential of azacitidine was tested in in vitro bacterial systems Salmonella typhimurium strains TA100 and several strains of trpE8, Escherichia coli strains WP14 Pro, WP3103P, WP3104P, and CC103; in in vitro forward gene mutation assay in mouse lymphoma cells and human lymphoblast cells; and in an in vitro micronucleus assay in mouse L5178Y lymphoma cells and Syrian hamster embryo cells. Azacitidine was mutagenic in bacterial and mammalian cell systems. The clastogenic effect of azacitidine was shown by the induction of micronuclei in L5178Y mouse cells and Syrian hamster embryo cells.

Administration of azacitidine to male mice at 9.9 mg/$m^2$ (approximately 9% the recommended human daily dose on a mg/$m^2$ basis) daily for 3 days prior to mating with untreated female mice resulted in decreased fertility and loss of offspring during subsequent embryonic and postnatal development. Treatment of male rats 3 times per week for 11 or 16 weeks at doses of 15-30 mg/$m^2$ (approximately 20%-40%, the recommended human daily dose on a mg/m basis) resulted in decreased weight of the testes and epididymides, and decreased sperm counts accompanied by decreased pregnancy rates and increased loss of embryos in mated females. In a related study, male rats treated for 16 weeks at 24 mg/$m^2$ resulted in an increase in abnormal embryos in mated females when examined on day 2 of gestation.

## 6. Pharmaceutical particulars

**6.1 List of Excipients**

Mannitol
Acetonitrile
Water for Injection

**6.2 Incompatibilities**

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.5.

**6.3 Shelf life**

Unopened powder vial:
2 years

After reconstitution:
**Subcutaneous Administration**

**Suspension Stability:** Azacitidine reconstituted with non-refrigerated water for injection for subcutaneous administration may be stored for up to 1 hour at 25°C (77°F) or for up to 8 hours between 2°C and 8°C (36°F and 46°F); when reconstituted with refrigerated (2ºC - 8ºC, 36ºF - 46ºF) water for injection, it may be stored for 22 hours between 2°C and 8°C (36°F and 46°F).

**Intravenous Administration**

**Solution Stability:** Azacitidine reconstituted for intravenous administration may be stored at 25°C (77°F), but administration must be completed within 1 hour of reconstitution.

**6.4 Special precautions for storage**

Unopened vials

Store below $30^0$C.

Reconstituted Medicinal Product:

For storage conditions after reconstitution of the medicinal product, see section 6.2.

**6.5 Nature and contents of container**

USP type-1 clear moulded glass vial

**6.6 Special precautions for disposal and other handling**

Recommendations for safe handling

Azacitidine is a cytotoxic medicinal product and, as with other potentially toxic compounds, caution should be exercised when handling and preparing azacitidine suspensions. Procedures for proper handling and disposal of anticancer medicinal products should be applied.

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

**7. Marketing Authorisation holder**

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**8. Marketing Authorisation Number**

H2022/CTD8810/18220

**9. Date of First Authorisation/Renewal of the Authorisation**

22/07/2022

**10. Date of Revision of the Text**

22/07/2022