SUMMARY OF PRODUCT CHARACTERISTICS

Azacitidine for Injection, 100 mg/Vial

1. NAME OF THE MEDICINAL PRODUCT

Azacitidine for Injection, 100 mg/Vial

Avoxred

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains Azacitidine 100mg

3. PHARMACEUTICAL FORM

Powder for solution for Injection

4. CLINICAL PARTICULARS

4.1 Indications:

1. Myelodysplastic Syndromes (MDS)

Azacitidin is indicated for treatment of adult patients with the following French-AmericanBritish (FAB) myelodysplastic syndrome subtypes: refractory anemia (RA) or refractory anemia with ringed sideroblasts (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).

2. Juvenile Myelomonocytic Leukemia (JMML)

Azacitidin is indicated for the treatment of pediatric patients aged one month and older with newly diagnosed JMML.

4.2 Posology and Administration:

Important Administration Instructions

Do not substitute Azacitidine injection for oral azacitidine. The indications and dosing regimen for Azacitidine injection differ from that of oral azacitidine

First Treatment Cycle for Adults

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.

Subsequent Treatment Cycles for Adults

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, and delay or reduce dosage if necessary.

Pediatric Patients with JMML

Table 1: Dosage and Administration for Pediatric Patients (JMML)

Pediatric Patients with JMML	Recommended Dose
Age 1 month to less than 1 year OR weighing less than 10 kg	2.5 mg/kg
Age 1 year and older AND weighing 10 kg or greater	75 mg/m^2

Azacitidine Injection is administered as an intravenous infusion daily for 7 days in a 28-day cycle. Patients should be treated for a minimum of 3 cycles and maximum of 6 cycles.

A delay in dose not exceeding 14 days can be considered for non-hematologic toxicities.

Monitor patients for hematologic response and renal toxicities, and delay or reduce dosage if necessary. Treatment may be continued up to six cycles as long as the patient continues to benefit.

Dosage Adjustment Based on Hematology Laboratory Values

- For adult patients with baseline (start of treatment) WBC greater than or equal to 3 x10^9/L, ANC greater than or equal to 1.5 x10^9/L, and platelets greater than or equal to 75 x10^9/L, adjust the dose as follows, based on nadir counts for any given cycle:

Nadir Counts %		Dose in the Next Course
ANC (x10^9/L)	Platelets (x10^9/L)	
Less than 0.5	Less than 25	50%
0.5 – 1.5	25-50	67%
Greater than 1.5	Greater than 50	100%

- For adult patients whose baseline counts are WBC less than 3 x10^9/L, ANC less than 1.5 x10^9/L, or platelets less than 75 x10^9/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
% Dose in the Next Course			
50 -75	100	50	33
Greater than 75	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%.

Pediatric Patients with JMML

As hematological toxicity will be difficult to assess and to differentiate from the natural course of the underlying disorder, dose reductions are not recommended due to hematological toxicity within the first 3 cycles. However, if the patient has a neutrophil count of less than 0.5 $x10^9$/L at end of Cycle 3 or on Day 1 of Cycles 5 or 6, discontinue the treatment.

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.

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.

Instructions for Subcutaneous Administration

Reconstitute Azacitidine Injection aseptically with 4 mL Sterile Water for Injection, USP to obtain a concentration of 25 mg/mL. Inject the diluent slowly into the vial. Vigorously shake or roll the vial until a uniform suspension is achieved. The suspension will be cloudy. 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. See Table 2 for suspension stability storage timelines based on the temperature of the diluent for delayed subcutaneous administration.

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 Injection 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.

Table 2 Suspension Stability: Storage timelines based on the temperature of the diluent for suspension stability storage:

Suspension Stability Storage timelines	
Diluent	Storage Temperature/Duration
Room temperature (25°C / 77°F) Sterile Water for Injection, USP	Store at room temperature at 25°C (77°F) for up to 1 hour or refrigerated at 2°C to 8°C (36°F to 46°F) for up to 8 hours.
Cold (2°C to 8°C / 36°F to 46°F) Sterile Water for Injection, USP	Store refrigerated at 2°C to 8°C (36°F to 46°F) for up to 22 hours.

Instructions for Intravenous Administration

Parenteral drug product should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use the product if there is evidence of particulate matter or discoloration.

Adult Patients with MDS

Reconstitute the appropriate number of Azacitidine Injection vials to achieve the desired dose. Reconstitute each vial with 10 mL Sterile Water for Injection, USP. 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.

Withdraw the required amount of Azacitidine Injection solution to deliver the desired dose and inject into a 50 -100 mL infusion bag of either 0.9% Sodium Chloride Injection, USP or Lactated Ringer' s Injection, USP.

Pediatric Patients with JMML

For pediatric patients with JMML, withdraw the required amount of Azacitidine Injection solution to deliver the desired dose and inject into an infusion bag (volume up to 100 mL) of either 0.9% Sodium Chloride Injection, USP or Lactated Ringer' s Injection, USP to achieve a final Azacitidine Injection concentration between 0.9 mg/mL and 4 mg/mL.

Intravenous Solution Incompatibility

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

Intravenous Administration

Azacitidine Injection 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 Injection vial.

Solution Stability:

Azacitidine Injection reconstituted and diluted for intravenous administration may be stored at 25°C (77°F), but administration must be completed within 1 hour of reconstitution.

4.3 Contraindications:

Azacitidine is contraindicated in patients with advanced malignant hepatic tumors

Azacitidine A is contraindicated in patients with a known hypersensitivity to azacitidine or mannitol.

4.4 Special warnings and precautions for use

Risks of Substitution with Other Azacitidine Products

Due to substantial differences in the pharmacokinetic parameters, the recommended dose and schedule for azacitidine injection are different from those of oral azacitidine products. Treatment of patients using azacitidine injection at the recommended dosage of oral azacitidine may result in a fatal adverse reaction. Treatment of patients using oral azacitidine at the doses recommended for azacitidine injection may not be effective. Do not substitute azacitidine injection for oral azacitidine.

Anemia, **Neutropenia and Thrombocytopenia**

Azacitidine causes anemia, neutropenia and thrombocytopenia in adult patients with MDS and in pediatric patients with JMML. Monitor complete blood counts frequently for response and/or toxicity, at a minimum, prior to each dosing cycle.

In adult patients with MDS, after administration of the recommended dosage for the first cycle, adjust dosage for subsequent cycles based on nadir counts and hematologic response.

In pediatric patients with JMML, dose reductions due to hematological toxicity are not recommended within the first 3 cycles as hematological toxicity will be difficult to assess and to differentiate from the natural course of the underlying disorder.

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. Monitor liver chemistries prior to initiation of therapy and with each cycle.

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

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 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 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.

Patients with renal impairment may be at increased risk for renal toxicity. Also, azacitidine and its metabolites are primarily excreted by the kidney. Therefore, monitor these patients closely for toxicity. Patients with MDS or pediatric patients with JMML and renal impairment were excluded from the clinical studies.

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.

Embryo-Fetal Toxicity

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.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with Azacitidine and for 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with Azacitidine and for 3 months after the last dose.

4.5 Interaction with other medicinal products

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

In vitro Studies

Cytochrome P450 (CYP) Enzymes: An in vitro study at azacitidine concentrations up to 100 μM (IV C_{max} = 10.6 μM) in human liver microsomes indicated that azacitidine does not cause any inhibition of CYP isoforms CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, or CYP2E1 at clinically achievable concentrations.

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.

Transporter Systems: An in vitro study with LLC-PK1 cells expressing P-glycoprotein (P-gp) indicated that azacitidine is not a substrate or inhibitor of P-gp.

Azacitidine does not inhibit, breast cancer resistance protein (BCRP), organic anion transporters

(OAT) OAT1 and OAT3, organic anion transporting polypeptides (OATP) OATP1B1 and OATP1B3, or organic cation transporter (OCT) OCT2 at clinically relevant concentrations.

4.6. Fertility, Pregnancy and Lactation

Pregnancy

Risk Summary

Based on its mechanism of action and findings in animals, azacitidine can cause fetal harm when administered to a pregnant woman. 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. 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^2 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 dose on a mg/m^2 basis), although treatment in the preimplantation period (on gestation days 1-3) had no adverse effect on the embryos. Azacitidine caused multiple fetal abnormalities in rats after a single IP dose of 3 to 12 mg/m^2 (approximately 8% the recommended human daily dose 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).

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 and the potential for serious adverse reactions in nursing infants from azacitidine, advise patients not to breastfeed during treatment with azacitidine and for 1 week after the last dose.

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.

Pregnancy Testing

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

Contraception

Females

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with azacitidine and for 6 months after the last dose.

Males

Advise males with female partners of reproductive potential to use effective contraception during treatment with azacitidine A and for 3 months after the last dose.

Infertility

Based on animal data, azacitidine could have an effect on male or female fertility

4.7. Effects on Ability to Drive and Use Machines

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

4.8. Undesirable Effects

Clinical Studies Experience

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.

MDS

The data described below reflect exposure to Azacitidine Injection in 443 patients with MDS 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).

In Studies 1, 2 and 3, a total of 268 patients were exposed to Azacitidine Injection, including 116 exposed for 6 cycles (approximately 6 months) or more and 60 exposed for greater than 12 cycles (approximately one year). Azacitidine Injection 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 Injection. 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 Injection doses of 75 mg/m^2.

Most Commonly Occurring Adverse Reactions (Subcutaneous or Intravenous Route) in Adult Patients with MDS: 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) in Adult Patients with MDS:

Discontinuation: leukopenia, thrombocytopenia, neutropenia.

Dose Held: leukopenia, neutropenia, thrombocytopenia, pyrexia, pneumonia, febrile neutropenia. Dose Reduced: leukopenia, neutropenia, thrombocytopenia.

Table 3 presents adverse reactions occurring in at least 5% of patients treated with Azacitidine Injection (subcutaneous) in Studies 1 and 2. It is important to note that duration of exposure was longer for the Azacitidine Injection -treated group than for the observation group: patients received Azacitidine Injection for a mean of 11.4 months while mean time in the observation arm was 6.1 months.

Table 3: Most Frequently Observed Adverse Reactions (≥5% in All Subcutaneous Azacitidine Injection Treated Patients; Studies 1 and 2)

	Number (%) of patients	
System Organ Class Preferred Term[a]	**All Azacitidine Injection [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 (16)	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)	9 (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)	(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 Injection, including patients after crossing over from observations.
c Includes adverse reactions from observation period only; excludes any adverse events after crossover to Azacitidine Injection

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

Table 4: Most Frequently Observed Adverse Reactions (≥5% in the Azacitidine Injection 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 Injection (N=175)**	**Best Supportive Care Only (N=102)**	**Azacitidine Injection (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 (0.6)	0
Pyrexia	53 (30)	18 (18)	8 (5)	1(1)
Infections and infestations				
Rhinitis	10 (5.7)	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 reports of the same preferred term from a patient were only counted once within each treatment.				

In Studies 1, 2 and 4 with subcutaneous administration of Azacitidine Injection, 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 Injection. 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 Injection, the following serious adverse reactions occurring at a rate of <5% were reported:

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

Cardiac disorders: atrial fibrillation, cardiac failure, cardiac failure congestive, cardiorespiratory 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.

Juvenile Myelomonocytic Leukemia (JMML)

The safety of Azacitidine Injection was evaluated in pediatric patients with JMML (N=18; 0.2-6.9 years old) in Study AZA-JMML-001. Patients received Azacitidine Injection as intravenous infusion daily for 7 days in a 28-day cycle.

Sixteen patients completed 3 cycles of therapy and 5 of the 16 patients completed 6 cycles. The median treatment duration was 12.3 weeks (range: 4.0 to 30.6 weeks) and the median total number of treatment cycles completed was 3 cycles (range: 1 to 6 cycles).

Serious adverse reactions occurred in 67% of patients who received Azacitidine Injection for JMML.

Permanent discontinuation of Azacitidine Injection due to an adverse reaction occurred in a single patient who had abdominal pain and acute respiratory distress syndrome.

The most common (≥30%) adverse reactions were pyrexia, rash, upper respiratory tract infection, and anemia.

Table 5 summarizes the adverse reactions in pediatric JMML.

Table 5: Most Frequently Observed Adverse Reactions (≥10%) in Pediatric Patients with JMML Receiving Azacitidine Injection in Study AZA-JMML-001

Adverse Reaction	**All Grades N=18 %**	**Grade 3 or 4 N=18 %**
General disorders and administration site conditions		
Pyrexia	61	0
Edema[a]	11	0
Skin and subcutaneous tissue disorders		
Rash[b]	44	0
Pruritus[c]	22	0
Dermatitis allergic	11	0
Petechiae	11	0
Infections and infestations		
Upper respiratory tract infection[d]	44	6
Febrile infection	11	6
Fungal infection[e]	11	6
Pneumonia[f]	11	0
Blood and lymphatic system disorders		
Anemia	39	33
Thrombocytopenia	28	22
Neutropenia	17	11
Febrile Neutropenia	11	6
Lymphadenopathy	11	6
Gastrointestinal disorders		
Vomiting	28	0
Abdominal pain[g]	22	11
Constipation	22	0
Diarrhea	22	6
Hemorrhage[h]	11	0

Nausea	11	0
Ascites	11	6
Respiratory, thoracic and mediastinal disorders		
Cough	22	0
Epistaxis	17	6
Metabolism and nutrition disorders		
Hyperuricemia	17	0
Fluid retention	11	0
Musculoskeletal and connective tissue disorders		
Musculoskeletal pain[i]	11	0

a Grouped term includes: face edema, generalized edema, edema peripheral.
b Grouped term includes: rash, rash macular, dermatitis bullous, rash maculo-papular, rash papular, rash pruritic.
c Grouped term includes: pruritis, pruritis generalized.
d. Grouped term includes: influenza, nasopharyngitis, Parainfluenzae virus infection, respiratory tract infection, rhinitis, upper respiratory tract infection, and viral upper respiratory tract infection
e. Grouped term includes: anal candidiasis, Candida infection, oral candidiasis.
[f] Grouped term includes: lung infection, pneumonia respiratory syncytial viral.
[g] Grouped term includes: abdominal pain, abdominal pain upper.
[h] Grouped term includes: mouth hemorrhage, rectal hemorrhage.
[i] Grouped term includes: back pain, musculoskeletal pain, non-cardiac chest pain, pain in extremity.

Postmarketing Experience

The following adverse reactions have been identified during postmarketing use of Azacitidine Injection. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Interstitial lung disease
- Tumor lysis syndrome
- Injection site necrosis
- Sweet' s syndrome (acute febrile neutrophilic dermatosis)
- Necrotizing fasciitis (including fatal cases)
- Differentiation syndrome
- Pericardial effusion
- Pericarditis
- Cutaneous vasculitis

Reporting of suspected adverse reactions: Healthcare professionals are requested to report any suspected adverse reactions via pharmacy and poisons board, pharmacovigilance Electronic Reporting System (PvERS) https://pv.pharmacyboardkenya.org

4.9 Overdose

One case of overdose with azacitidine injection 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 events resolved without sequelae, and the correct dose was resumed the following day. 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 azacitidine injection overdosage.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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.

In pediatric patients with JMML post azacitidine treatment (75 mg/m^2 or 2.5 mg/kg), reductions in genome-wide DNA methylation (global DNA methylation scores) were attained in bone marrow granulocytes during the first treatment cycle, confirming the DNA-hypomethylating activity of azacitidine.

5.2 Pharmacokinetic properties

The pharmacokinetics of azacitidine were studied in 6 adult patients with MDS 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 after subcutaneous administration.

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 Cmax 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 doseregimen does not result in drug accumulation with intravenous or subcutaneous administration.

Elimination

Metabolism

An in vitro study of azacitidine incubation in human liver fractions indicated that azacitidine is not metabolized by the cytochrome P450 (CYP) enzymes. Azacitidine undergoes spontaneous hydrolysis and deamination mediated by cytidine deaminase.

Excretion

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 accounted for <1% of administered radioactivity over 3 days. Mean excretion of radioactivity in 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

The effects of hepatic impairment, gender, or race/ethnicity on the pharmacokinetics of intravenous and subcutaneous azacitidine have not been studied.

Pediatric Patients

Following intravenous administration of a 75 mg/m^2 or 2.5 mg/kg dose in pediatric patients with JMML, population pharmacokinetic analysis determined that azacitidine rapidly reached a geometric mean C_{max} of 4510 ng/mL (CV%: 65.6%), and a geometric mean AUC_{0-24} of 1550 ng h/mL (CV%: 56.6%). The geometric mean $t_{1/2}$ was 0.3 hours (CV%: 59.9%), and the geometric mean clearance was 21.8 L/h (CV%: 102.2%).

Population PK analysis of 6 adults and 34 pediatric patients did not identify any clinically meaningful differences in the pharmacokinetics of intravenous azacitidine according to sex (62.5% male), and tumor type (MDS, JMML, AML). Increased clearance was associated with increased baseline body weight (4.6 to 102 kg). BSA or body weight-based dosing resulted in consistent plasma azacitidine exposure in pediatric patients with JMML across the body weight range (4.6 to 18.5 kg) and age range (0.2 to 6.9 years).

Patients with Renal Impairment

In adult 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.

5.3 Pre-Clinical Safety Data

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^2 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^2 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, Water for Injection, Nitrogen.

6.2 Incompatibilities

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

6.3 Shelf-life

24 Months

6.4 Special precautions for storage

Unopened vials

This medicinal product does not require any special storage conditions.

Reconstituted suspension

For storage conditions after reconstitution of the medicinal product

6.5 Nature and contents of container

Primary packaging:

Container – 30 mL USP Type I Flint Tubular glass vial

Stopper – 20mm Bromobutyl FM 460/0 V9154 rubber stoppers

Seal – 20mm flip-off seal, violet

6.6 Instructions for use, handling and disposal

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.

7. MARKETING AUTHORIZATION

Dr. Reddy's Laboratories Limited,

D.No. 8-2-337,
Road No. 3, Banjara Hills,
Hyderabad - 500034.

Telangana, India.

8. MARKETING AUTHORISATION NUMBER (S)

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2024

10. Date of revision of the text

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