PRODUCT MONOGRAPH

Pr Reddy-Azacitidine

Azacitidine for Injection
100 mg azacitidine per vial

Antineoplastic Agent Pyrimidine Analogue

DIN Owner:
Dr. Reddy's Laboratories Limited
Bachupally–500 090 INDIA
INDIA

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Imported By: Dr. Reddy's Laboratories Canada Inc.,
2425 Matheson Blvd East, #754
Mississauga, ON L4W 5K4 CANADA

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PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	All Nonmedicinal Ingredients
Subcutaneous	Lyophilized powder, 100 mg azacitidine per vial	Mannitol

INDICATIONS AND CLINICAL USE

Reddy-Azacitidine is indicated for the treatment of adult patients who are not eligible for hematopoietic stem cell transplantation with:

- Intermediate-2 and High-risk Myelodysplastic Syndrome (MDS) according to the International Prognostic Scoring System (IPSS),

- Acute Myeloid Leukemia (AML) with 20-30 % blasts and multi lineage dysplasia, according to World Health Organization (WHO) classification.

Geriatrics (≥ 65 years of age):
No overall differences in safety or effectiveness of Azacitidine for Injection were observed between younger patients and patients ≥ 65 years of age. Greater sensitivity of some older individuals cannot be ruled out. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function.

Pediatrics (< 18 years of age):
The safety and effectiveness of Azacitidine for Injection in children and adolescents have not been established.

CONTRAINDICATIONS

- Patients who are hypersensitive to azacitidine or to any ingredient in the formulation or component of the container. For a complete listing, see **DOSAGE FORMS, COMPOSITION AND PACKAGING**.

- Advanced malignant hepatic tumors

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Thrombocytopenia (see **WARNINGS AND PRECAUTIONS, Hematologic**)
- Renal failure, including fatalities (see **WARNINGS AND PRECAUTIONS, Renal** and **Monitoring and Laboratory Tests**)

Reddy-Azacitidine should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents.

General

Treatment with Reddy-Azacitidine may require supportive care sufficient to protect a patient from serious bleeding, infection and less serious nausea and vomiting.

Carcinogenesis and Mutagenesis

In vitro studies demonstrated that azacitidine is mutagenic and clastogenic in bacterial and mammalian cell systems. Azacitidine induced tumors of the hematopoietic system in female mice, when administered intraperitoneally 3 times per week at 2.2 mg/kg (6.6 mg/m^2) for 52 weeks. An increased incidence of tumors in the lymphoreticular system, lung, mammary gland, and skin was seen in mice treated with azacitidine administered intraperitoneally once a week at 2.0 mg/kg (6 mg/m^2) for 50 weeks. A tumorigenicity study in rats revealed an increased incidence of mammary and testicular tumors at 2.6 mg/kg (15.6 mg/m^2) when administered intraperitoneally 3 times per week for 34 weeks (see **TOXICOLOGY**).

Cardiovascular

Patients with a history of severe congestive heart failure, clinically unstable cardiac disease or pulmonary disease were excluded from the pivotal clinical study and therefore the safety and efficacy of Azacitidine for Injection in these patients have not been established.

No thorough clinical QT/QTc study or *in vitro* studies (hERG, canine Purkinje fiber assay) were performed to rule out the effect of Azacitidine for Injection on QT prolongation. An *in vivo* safety pharmacology study in dogs receiving azacitidine reported increased QTc interval, but interpretation of this study is limited by confounding effects associated with toxicity (see **TOXICOLOGY**).

Endocrine and Metabolism

There have been reports of Tumor Lysis Syndrome (TLS) in patients treated with Azacitidine for Injection in the postmarketing setting. Patients at risk for TLS are those with high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

Hematologic

Treatment with Azacitidine for Injection is associated with anemia, neutropenia and

thrombocytopenia, particularly during the first 2 cycles. Complete blood counts should be performed as needed to monitor response and toxicity, but at least prior to each treatment cycle (see **Monitoring and Laboratory Tests**). After administration of the recommended dose for the first cycle, the dose for subsequent cycles should be reduced or its administration delayed based on nadir counts and hematological response (see **DOSAGE AND ADMINISTRATION**). Patients should be advised to promptly report febrile episodes. Patients and physicians should be observant for signs and symptoms of bleeding, particularly in case of pre-existing or treatment-related thrombocytopenia. Physicians should be prepared to provide appropriate supportive measures (e.g., transfusions for anemia and thrombocytopenia, growth factors and/or prophylactic antibiotics for neutropenia).

Hepatic/Biliary/Pancreatic

Patients with extensive tumor burden due to metastatic disease have been rarely reported to experience progressive hepatic coma and death during Azacitidine for Injection treatment, especially in such patients with baseline serum albumin < 30 g/L. Reddy-Azacitidine is contraindicated in patients with advanced malignant hepatic tumors (see **CONTRAINDICATIONS**).
Safety and effectiveness of Azacitidine for Injection in patients with MDS and hepatic impairment have not been studied as these patients were excluded from the clinical trials.

Renal

Renal abnormalities ranging from elevated serum creatinine to renal failure and death were reported rarely in patients treated with intravenous Azacitidine for Injection in combination with other chemotherapeutic agents. Severe renal tubular dysfunction may infrequently accompany Reddy-Azacitidine therapy and may be manifested as hypophosphatemia, hypokalemia, or hyponatremia, with or without increases in serum creatinine and blood urea nitrogen (BUN). In addition, renal tubular acidosis, defined as a fall in serum bicarbonate to < 20 mmol/L in association with an alkaline urine and hypokalaemia (serum potassium < 3 mmol/L) was reported in 5 subjects with chronic myelogenous leukemia (CML) treated with Azacitidine for Injection and etoposide. Serum electrolytes, bicarbonate (serum CO_2), creatinine, and BUN should be monitored periodically (see **Monitoring and Laboratory Tests**). If unexplained reductions in serum bicarbonate (< 20 mmol/L) or elevations of serum creatinine or BUN occur, the dose should be reduced or administration delayed (see **DOSAGE AND ADMINISTRATION**).
Patients with renal impairment should be closely monitored for toxicity since Reddy-Azacitidine and/or its metabolites are primarily excreted through the kidney.

Sexual Function/Reproduction

Men should be advised not to father a child while receiving treatment and for 6 months following the last dose. Females of childbearing potential must use effective contraception during and up to 3 months after treatment.

Skin and Subcutaneous Tissue
Necrotizing fasciitis, including fatal cases, has been reported in patients treated with Azacitidine

for injection. Reddy-Azacitidine therapy should be discontinued in patients who develop necrotizing fasciitis, and appropriate treatment should be promptly initiated.
Reports of injection site necrosis have been received for patients treated with Azacitidine for Injection in the postmarketing setting. Patients should be monitored for signs of injection site necrosis and appropriate management taken as warranted.

Special Populations

Pregnant Women: In mice and rat developmental toxicity studies Azacitidine for injection caused multiple fetal abnormalities, including CNS anomalies (exencephaly/encephalocele), limb anomalies (micromelia, club foot, syndactyly, oligodactyly) and others (microphthalmia, micrognathia, gastroschisis, edema, and rib abnormalities) and fetal deaths (see **TOXICOLOGY**).

There are no adequate data on the use of Azacitidine for injection in pregnant women. The potential risk for humans is unknown. Reddy-Azacitidine should not be used during pregnancy. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Reddy-Azacitidine. If the patient becomes pregnant while taking Azacitidine for injection, she should be apprised of the potential hazard to the fetus.

Nursing Women: It is not known whether azacitidine or its metabolites are excreted in human milk. Due to the potential for carcinogenicity shown for azacitidine in animal studies and the potential for serious adverse reactions in the nursing child, mothers should be advised not to breast feed while undergoing therapy with Reddy-Azacitidine.

Pediatrics (<18 years of age): The safety and effectiveness of Azacitidine for Injection in children and adolescents have not been established. In the clinical trial program, no patients under 18 years of age were treated.

Geriatrics (> 65 years of age): Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function.

Monitoring and Laboratory Tests

Liver function tests and serum creatinine should be determined prior to initiation of therapy and prior to each treatment cycle. Complete blood counts should be performed prior to initiation of therapy and as needed to monitor response and toxicity, but at a minimum, prior to each treatment cycle. Serum electrolytes, bicarbonate (serum CO_2), creatinine, and BUN should be monitored periodically.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Adverse reactions considered to be possibly or probably related to the administration of Azacitidine for Injection have occurred in 97 % of patients.

The most commonly reported adverse reactions with Azacitidine for Injection treatment were

hematological reactions including thrombocytopenia, neutropenia and leukopenia (usually Grade 3-4), gastrointestinal events including nausea, vomiting (usually Grade 1-2) or injection site reactions (usually Grade 1-2).

The most common serious adverse reactions (> 2 %) noted from the pivotal study and also reported in the supporting studies included febrile neutropenia (8.0 %) and anemia (2.3 %). Other less frequently reported serious adverse reactions (< 2 %) included neutropenic sepsis, pneumonia, thrombocytopenia and hemorrhagic events (e.g., cerebral hemorrhage).

Adverse reactions most frequently resulting in discontinuation or dose reduction were leukopenia, thrombocytopenia, and neutropenia. Adverse reactions most frequently resulting in the dose being held were leukopenia, neutropenia, thrombocytopenia, pyrexia, pneumonia, and febrile neutropenia.

Clinical Trial Adverse Drug Reactions

Phase 3 Pivotal International Open-Label Randomized Survival Study in Higher Risk MDS (AZA-001)

The pivotal clinical study (AZA-001) was an international, multicenter, open-label, randomized trial in MDS patients with refractory anemia with excessive blasts (RAEB), RAEB in transformation (RAEB-T) or modified chronic myelomonocytic leukemia (CMMoL) according to the French American British (FAB) classification and Intermediate-2 and High risk according to IPSS classification. Of the 358 patients enrolled in the study, 179 were randomized to receive Azacitidine for Injection plus best supportive care (BSC) and 179 were randomized to receive conventional care regimens (CCR) plus BSC (105 to BSC alone, 49 to low dose cytarabine and 25 to chemotherapy with cytarabine and anthracycline).

Azacitidine for Injection was administered subcutaneously (SC) at a dose of 75 mg/m^2 daily for 7 consecutive days every 28 days (which constituted one cycle of therapy).

In AZA-001 the median cycle length for patients treated with Azacitidine for Injection was 34.0 days, suggesting that investigators were delaying the start of the next treatment cycle consistent with protocol-specified dosing recommendations based on hematological toxicities. The median number of treatment cycles was 9.

Patients treated with Azacitidine for Injection remained on treatment longer than those receiving best supportive care (BSC) and thus had a longer median treatment period (10.43 months) compared with BSC only (6.16 months).

The most common serious adverse events that were assessed as at least possibly related to Azacitidine for Injection in Study AZA-001 (≥ 3 patients) included febrile neutropenia (8.0%); anemia (2.3%); as well as neutropenic sepsis, pneumonia, and thrombocytopenia (1.7% each). Serious treatment-related hemorrhagic adverse reactions (e.g., cerebral hemorrhage in 1.1 % of patients) were also considered medically important.

In Study AZA-001, the frequency of adverse events leading to discontinuation of Azacitidine for Injection or to reduction of the dose was 12.6% and 11.4%, respectively. Therapy with Azacitidine for Injection was temporarily interrupted in 46.9% of patients. The Treatment Emergent Adverse Events (TEAEs) most frequently leading to interruption were neutropenia, 18.3%; thrombocytopenia 12.6%, pneumonia 4.0% and pyrexia 2.9%. The percentage for all other TEAEs that led to interruption was < 2%.

The most common clinical intervention as a result of adverse drug reactions in Azacitidine for Injection-treated patients was treatment with a concomitant medication in 96.0% of Azacitidine for Injection patients (Study AZA-001).

There were 12% (21/175) on treatment deaths in the Azacitidine for Injection group compared with 18.6% (19/102) in the BSC group. In Azacitidine for Injection-treated patients, the adverse events that most frequently led to death were from the infections and infestations SOC including pneumonia and sepsis in 5 patients each (2.9%); cerebral hemorrhage in 4 patients (2.3%), and AML or MDS in 3 patients each (1.7%). Note that some of these patients experienced more than 1 treatment emergent adverse event resulting in death. Of the 21 on-treatment deaths in the Azacitidine for Injection group, 7 were assessed as possibly related to Azacitidine for Injection (of which 1 was considered to be possibly related to underlying disease as well).

Table 1: Most Frequently Observed Adverse Reactions (≥ 5.0% in the Azacitidine for Injection Treated Patients and the Percentage with NCI CTC Grade 3/4 Reactions; AZA-001)

System Organ Class Preferred Term[a]	Number (%) of Patients			
	Any Grade		Grade 3/4	
	Azacitidine for Injection (N=175)	Best Supportive Care Only (N=102)	Azacitidine for Injection (N=175)	Best Supportive Care Only (N=102)
Blood and lymphatic system disorders				
Thrombocytopenia	122 (69.7)	35 (34.3)	102 (58.3)	29 (28.4)
Neutropenia	115 (65.7)	29 (28.4)	107 (61.1)	22 (21.6)
Anemia	90 (51.4)	45 (44.1)	24 (13.7)	9 (8.8)
Leukopenia	32 (18.3)	2 (2.0)	26 (14.9)	1 (1.0)
Febrile neutropenia	24 (13.7)	10 (9.8)	22 (12.6)	7 (6.9)
Gastrointestinal disorders				
Constipation	88 (50.3)	8 (7.8)	2 (1.1)	0
Nausea	84 (48.0)	12 (11.8)	3 (1.7)	0
Vomiting	47 (26.9)	7 (6.9)	0	0
Abdominal pain	22 (12.6)	7 (6.9)	7 (4.0)	0
Dyspepsia	10 (5.7)	2 (2.0)	0	0
General disorders and administration site conditions				
Injection site erythema	75 (42.9)	0	0	0
Pyrexia	53 (30.3)	18 (17.6)	8 (4.6)	1 (1.0)

Injection site reaction	51 (29.1)	0	1 (0.6)	0
Fatigue	42 (24.0)	12 (11.8)	6 (3.4)	2 (2.0)
Injection site pain	33 (18.9)	0	0	0
Injection site hematoma	11 (6.3)	0	0	0
Injection site rash	10 (5.7)	0	0	0
Injection site induration	9 (5.1)	0	0	0
Injection site bruising	9 (5.1)	0	0	0
Infections and infestations				
Upper respiratory tract infection	16 (9.1)	4 (3.9)	3 (1.7)	0
Urinary tract infection	15 (8.6)	3 (2.9)	3 (1.7)	0
Rhinitis	10 (5.7)	1 (1.0)	0	0
Investigations				
Weight decreased	14 (8.0)	0	1 (0.6)	0
Metabolism and nutrition disorders				
Hypokalemia	11 (6.3)	3 (2.9)	3 (1.7)	3 (2.9)
Nervous system disorders				
Lethargy	13 (7.4)	2 (2.0)	0	1 (1.0)
Psychiatric disorders				
Insomnia	15 (8.6)	3 (2.9)	0	0
Anxiety	9 (5.1)	1 (1.0)	0	0
Renal and urinary disorders				
Hematuria	11 (6.3)	2 (2.0)	4 (2.3)	1 (1.0)
Respiratory, thoracic and mediastinal disorders				
Dyspnea	26 (14.9)	5 (4.9)	6 (3.4)	2 (2.0)
Pharyngolaryngeal pain	11 (6.3)	3 (2.9)	0	0
Dyspnea exertional	9 (5.1)	1 (1.0)	0	0
Skin and subcutaneous tissue disorders				
Pruritus	21 (12.0)	2 (2.0)	0	0
Petechiae	20 (11.4)	4 (3.9)	2 (1.1)	0
Rash	18 (10.3)	1 (1.0)	0	0
Erythema	13 (7.4)	3 (2.9)	0	0
Vascular disorders				
Hypertension	15 (8.6)	4 (3.9)	2 (1.1)	2 (2.0)

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

System organ classes and preferred terms are based on coding of adverse events using MedDRA

Supportive Cancer and Leukemia Group B (CALGB) studies CALGB 9221 and CALGB 8921

Study 9221 was a randomized, open-label, controlled trial carried out in 53 U.S. sites that compared the safety and efficacy of subcutaneous Azacitidine for Injection plus supportive care with supportive care alone ("observation") in patients with any of the five FAB subtypes of MDS: refractory anemia (RA), RA with ringed sideroblasts (RARS),RAEB, RAEB-T, and CMMoL. Study 8921 was a multi-center, open-label, single-arm study of 72 patients with RAEB, RAEB-T, CMMoL or AML.

For the combined supportive studies, the median average cycle length was comparable at 33.5 days. Table 2 presents adverse reactions occurring in at least 5% of patients treated with Azacitidine for Injection in the two supportive studies described above. The serious events observed in AZA-001 were also the most commonly reported (≥ 3 patients) treatment- related serious adverse events in the combined supportive 9221/8921 CALGB studies in Azacitidine for Injection-treated patients, in addition to pyrexia (6.8%).

It is important to note that duration of exposure was longer for the Azacitidine for Injection-treated group than for the observation group: patients received Azacitidine for Injection for a mean of 11.4 months while mean time in the observation arm was 6.1 months.

Table 2: Most Frequently Observed Adverse Reactions (≥ 5.0% in All SC Azacitidine for Injection Treated Patients; Studies 9221 and 8921)

System Organ Class Preferred Term[a]	Number (%) of Patients	
	All Azacitidine for Injection[b] (N=220)	Observation[c] (N=92)
Blood and lymphatic system disorders		
Anemia	153 (69.5)	59 (64.1)
Thrombocytopenia	144 (65.5)	42 (45.7)
Leukopenia	106 (48.2)	27 (29.3)
Neutropenia	71 (32.3)	10 (10.9)
Febrile neutropenia	36 (16.4)	4 (4.3)
Anemia aggravated	12 (5.5)	5 (5.4)
Gastrointestinal disorders		
Nausea	155 (70.5)	16 (17.4)
Vomiting	119 (54.1)	5 (5.4)
Diarrhea	80 (36.4)	13 (14.1)
Constipation	74 (33.6)	6 (6.5)
Abdominal tenderness	26 (11.8)	1 (1.1)
Gingival bleeding	21 (9.5)	4 (4.3)
Stomatitis	17 (7.7)	0
Loose stools	12 (5.5)	0
Mouth hemorrhage	11 (5.0)	1 (1.1)

General disorders and administration site conditions		
Pyrexia	114 (51.8)	28 (30.4)
Injection site erythema	77 (35.0)	0
Injection site pain	50 (22.7)	0
Chest pain	36 (16.4)	5 (5.4)
Injection site bruising	31 (14.1)	0
Injection site reaction	30 (13.6)	0
Malaise	24 (10.9)	1 (1.1)
Lethargy	17 (7.7)	2 (2.2)
Injection site pruritus	15 (6.8)	0
Injection site granuloma	11 (5.0)	0
Injection site pigmentation changes	11 (5.0)	0
Injection site swelling	11 (5.0)	0
Infections and infestations		
Nasopharyngitis	32 (14.5)	3 (3.3)
Upper respiratory tract infection	28 (12.7)	4 (4.3)
Pneumonia	24 (10.9)	5 (5.4)
Injury, poisoning, and procedural complications		
Post procedural hemorrhage	13 (5.9)	1 (1.1)
Metabolism and nutrition disorders		
Anorexia	45 (20.5)	6 (6.5)
Musculoskeletal and connective tissue disorders		
Arthralgia	49 (22.3)	3 (3.3)
Myalgia	35 (15.9)	2 (2.2)
Chest wall pain	11 (5.0)	0
Nervous system disorders		
Headache	48 (21.8)	10 (10.9)
Dizziness	41 (18.6)	5 (5.4)
Psychiatric disorders		
Anxiety	29 (13.2)	3 (3.3)
Insomnia	24 (10.9)	4 (4.3)
Respiratory, thoracic and mediastinal disorders		
Dyspnea	64 (29.1)	11 (12.0)
Skin and subcutaneous tissue disorders		
Ecchymosis	67 (30.5)	14 (15.2)
Erythema	37 (16.8)	4 (4.3)
Rash	31 (14.1)	9 (9.8)
Urticaria	13 (5.9)	1 (1.1)
Dry skin	11 (5.0)	1 (1.1)
Skin nodule	11 (5.0)	1 (1.1)
Vascular disorders		
Petechiae	52 (23.6)	8 (8.7)
Hematoma	19 (8.6)	0

Hypotension	15 (6.8)	2 (2.2)

[a] Multiple reports 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 for Injection, including patients after crossing over from observations.

[c] Includes adverse reactions from observation period only; excludes any adverse events after crossover to Azacitidine for Injection. System organ classes and preferred terms are based on coding of adverse events using MedDRA.

In AZA-001 and two supporting clinical studies of Azacitidine for Injection (Study 9221 and Study 8921), 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 for Injection. Adverse reactions that tended to be more pronounced during the first 1 to 2 cycles of SC 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.

Less Common Clinical Trial Adverse Drug Reactions (<5%)

The list below contains the adverse reactions for which a causal relationship with Azacitidine for Injection treatment could reasonably be established. Frequencies given are based on the observations during the pivotal clinical study or two supporting clinical studies. The frequencies are defined using the CIOMS IV working group recommendation criteria:

Common (frequent) ≥1/100 and <1/10 (≥1% and <10%)

Uncommon (infrequent) ≥1/1000 and <1/100 (≥0.1% and <1%)

Blood and lymphatic system disorders:

Common: bone marrow failure, pancytopenia

Eye disorders:

Common: eye hemorrhage, conjunctival hemorrhage

Gastrointestinal disorders:

Common: gastrointestinal hemorrhage, hemorrhoidal hemorrhage, stomatitis, gingival bleeding

General disorders and administration site conditions:

Common: injection site inflammation, injection site discoloration, injection site nodule, injection site hemorrhage

Immune system disorders:

Uncommon: hypersensitivity reaction

Infections and infestations:

Common: neutropenic sepsis, sinusitis, pharyngitis, herpes simplex

Musculoskeletal and connective tissue disorders:

Common: musculoskeletal pain

Nervous system disorders:

Common: intracranial hemorrhage

Psychiatric disorders:

Common: confusional state

Skin and subcutaneous tissue disorders:

Common: purpura, alopecia, rash macular

Vascular disorders:

Common: hematoma

Post-Market Adverse Drug Reactions

An estimated nearly 247,000 patients were exposed to Azacitidine for Injection outside of sponsor-conducted clinical studies from May 2004 through 18 May 2015. Adverse reactions identified from other sources (including reports from post-marketing surveillance activities, non-sponsor-conducted clinical studies [e.g., investigator-initiated trials], other compassionate-use/named-patient use, registries, or the published literature) have generally been similar to those reported during clinical trials with Azacitidine for Injection. During other experience, serious adverse reactions reported in more than an isolated patient receiving Azacitidine for Injection and not previously described in the **ADVERSE REACTIONS** section include the following:

Blood and lymphatic system disorders:

- Hemorrhagic diathesis

Cardiac disorders:

- Atrial fibrillation, cardiac failure congestive, cardiac failure, pericardial effusion

Gastrointestinal disorders:

- Colitis, intestinal perforation, pancreatitis acute, subileus

General disorders and administration site conditions:

- Death, edema peripheral, sudden death, injection site necrosis

Hepatobiliary disorders:

- Hepatic failure, hepatitis, ascites, hyperbilirubinemia, jaundice

Infections and infestations:

- Sepsis, septic shock, infection, bacterial sepsis, abscess intestinal, cellulitis, pseudomonal sepsis, lower respiratory tract infection, bronchopulmonary aspergillosis, Clostridium difficile colitis, lobar pneumonia, lung infection pseudomonal

Injury, poisoning and procedural complications:

- Splenic rupture

Investigations:

- Blood creatinine increased, blood bilirubin increased, AST increased, ALT increased

Metabolism and nutrition disorders:

- Dehydration, hyperglycemia, hyponatremia, tumor lysis syndrome

Nervous system disorders:

- Grand mal convulsion

Renal and urinary disorders:

- Renal failure acute, renal failure

Respiratory, thoracic, and mediastinal disorders:

- Interstitial lung disease, pulmonary embolism, acute respiratory distress syndrome

Skin and subcutaneous tissue disorders:

- Leukocytoclastic vasculitis, pyoderma gangrenosum, Sweet's syndrome (acute febrile neutrophilic dermatosis), necrotizing fasciitis

DRUG INTERACTIONS

Overview

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

Based on *in vitro* data, azacitidine metabolism does not appear to be mediated by cytochrome P450 isoenzymes (CYPs) (see **PHARMACOKINETICS**). Therefore CYP inhibitors and inducers are unlikely to have any impact on the metabolism of azacitidine.

Clinically significant inhibitory or inductive effects of azacitidine on cytochrome P450 enzymes are unlikely.

Drug-Drug Interactions

Interactions with other drugs have not been established.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions

No studies of the effects on the ability to drive and use machines have been performed. Patients should be advised that they may experience undesirable effects such as fatigue, during treatment with Reddy-Azacitidine. Therefore, caution should be recommended when driving a car or operating machines.

DOSAGE AND ADMINISTRATION

Dosing Considerations

- Patients should be premedicated with anti-emetics for nausea and vomiting.
- Reddy-Azacitidine is for subcutaneous use only.
- Azacitidine for Injection has not been studied in patients with impaired hepatic function.

- Dosage given should be adjusted according to tolerability as described below.

Recommended Dose and Dosage Adjustment

Recommended dose

The recommended starting dose for the first treatment cycle, for all patients regardless of baseline hematology laboratory values, is 75 mg/m^2 of body surface area, injected subcutaneously, daily for 7 consecutive days, followed by a rest period of 21 days (28-day treatment cycle).

It is recommended that patients be treated for a minimum of 6 cycles unless unacceptable toxicities occur after dose delays / adjustments or standard supportive care such as transfusions, growth factors or antibiotics have proved to be unsuccessful. Treatment should be continued as long as the patient continues to benefit or until disease progression.

Patients should be monitored for hematologic response/toxicity and renal toxicities (see **WARNINGS and PRECAUTIONS**); a delay in starting the next cycle or a dose reduction as described below may be necessary.

- *Renal impairment*: Reddy-Azacitidine can be administered to patients with renal impairment without initial dose adjustment. If unexplained reductions in serum bicarbonate levels to less than 20 mmol/L occur, the dose should be reduced by 50 % on the next cycle. If unexplained elevations in serum creatinine or BUN to ≥ 2 fold above baseline values and above ULN occur, the next cycle should be delayed until values return to normal or baseline. The dose should be reduced by 50 % on the next treatment cycle (see **WARNINGS AND PRECAUTIONS**). Patients with renal impairment should be closely monitored for toxicity since Reddy-Azacitidine and/or its metabolites are primarily excreted through the kidney.

- *Hepatic impairment:* Patients with impaired liver function were excluded from the pivotal clinical trial. These patients should be treated with caution. Reddy-Azacitidine is contraindicated in patients with advanced malignant hepatic tumors (see **WARNINGS AND PRECAUTIONS** and **CONTRAINDICATIONS**).

Dose adjustment due to hematological toxicity

Hematological toxicity is defined as the lowest count reached in a given cycle (nadir) if platelets fall below 50.0 x 10^9/L and/or absolute neutrophil count (ANC) below 1 x 10^9/L.

Recovery is defined as an increase of cell line(s) where hematological toxicity was observed of at least half of the difference of nadir and the baseline count plus the nadir count (i.e., blood count at recovery ≥ Nadir Count + (0.5 x [Baseline count – Nadir count]).

Patients without reduced baseline blood counts (i.e. White Blood Cells (WBC) ≥ 3.0 x 10^9/L and ANC ≥ 1.5 x 10^9/L, and platelets ≥ 75.0 x 10^9/L) prior to the first treatment

If hematological toxicity is observed following Reddy-Azacitidine treatment, the next cycle of

Reddy-Azacitidine therapy should be delayed until the platelet count and the ANC have recovered. If recovery is achieved within 14 days, no dose adjustment is necessary. However, if recovery has not been achieved within 14 days, the dose should be reduced according to Table 3. Following dose modifications, the cycle duration should return to 28 days.

Table 3: Dose Modifications due to hematological toxicity, Patients without reduced baseline blood counts

Nadir counts		% Dose in the next cycle, if recovery[a] is not achieved within 14 days
ANC ($x\ 10^9$/L)	Platelets ($x\ 10^9$/L)	
≤ 1.0	≤ 50.0	50 %
> 1.0	> 50.0	100 %

[a] Recovery = counts ≥ Nadir count + (0.5 x [Baseline count - Nadir count])

Patients with reduced baseline blood counts (i.e. WBC < 3.0 x 10^9/L or ANC < 1.5 x 10^9/L or platelets < 75.0 x 10^9/L) prior to the first treatment

Following Reddy-Azacitidine treatment, if the decrease in WBC or ANC or platelets from that prior to treatment is less than 50 %, or greater than 50 % but with an improvement in any cell line differentiation, the next cycle should not be delayed and no dose adjustment made.

If the decrease in WBC or ANC or platelets is greater than 50 % from that prior to treatment, with no improvement in cell line differentiation, the next cycle of Reddy-Azacitidine therapy should be delayed until the platelet count and the ANC have recovered. If recovery is achieved within 14 days, no dose adjustment is necessary. However, if recovery has not been achieved within 14 days, bone marrow cellularity should be determined. If the bone marrow cellularity is > 50 %, no dose adjustments should be made. If bone marrow cellularity is ≤ 50 %, treatment should be delayed and the dose reduced according to Table 4:

Table 4: Dose Modifications due to hematological toxicity, Patients with reduced baseline blood counts

Bone marrow cellularity	% Dose in the next cycle if recovery is not achieved within 14 days	
	Recovery[a] ≤ 21 days	Recovery[a] > 21 days
15-50 %	100 %	50 %
< 15 %	100 %	33 %

[a] Recovery = counts ≥ Nadir count + (0.5 x [Baseline count - Nadir count])

Following dose modifications, the cycle duration should return to 28 days.

Missed Dose

If a dose is missed during the 7-day cycle, it should not be administered at the same time as the next dose, but should be added to the end of the current dosing cycle.

Administration

Reconstituted Reddy-Azacitidine should be injected subcutaneously (insert the needle at a 45-90° angle) using a 25-gauge needle into the upper arm, thigh or abdomen. Doses greater than 4 mL should be injected into two separate sites. Injection sites should be rotated. New injections should be given at least 2.5 cm from the previous site and never into areas where the site is tender, bruised, red, or hardened.

Calculation of an individual dose

The total dose, according to the body surface area (BSA) can be calculated as follows: Total dose (mg) = Dose (mg/m^2) x BSA (m^2)

Table 5 is provided only as an example of how to calculate individual Reddy-Azacitidine doses based on an average BSA value of 1.8 m^2.

Table 5: Example of calculation of an individual dose

Dose mg/m^2 (% of recommended starting dose)	**Total dose based on BSA value of 1.8 m^2**	**Number of vials required**	**Total volume of reconstituted suspension required**
75 mg/m^2 (100 %)	135 mg	2 vials	5.4 mL
37.5 mg/m^2 (50 %)	67.5 mg	1 vial	2.7 mL
25 mg/m^2 (33 %)	45 mg	1 vial	1.8 mL

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

Reconstitution:

Table 6: Reconstitution

Vial Size	**Volume of Diluent to be Added to Vial**	**Approximate Available Volume**	**Nominal Concentration per mL**
100 mg	4 mL water for injection	4 mL	25 mg/mL

Reconstitution procedure

1. The following supplies should be assembled:
    - Vial(s) of Reddy-Azacitidine; vial(s) of water for injection; nonsterile surgical gloves;
    - Alcohol wipes; 5 mL injection syringe(s) with needle(s).
2. 4 mL of water for injection should be drawn into the syringe, making sure to purge any air

trapped within the syringe.

3. The needle of the syringe containing the 4 mL of water for injection should be inserted through the rubber top of the Reddy-Azacitidine vial followed by injection of the water for injection into the vial.

4. Following removal of the syringe and needle, the vial should be vigorously shaken until a uniform cloudy suspension is achieved. Do not filter the suspension after reconstitution. Doing so could reduce or remove the active substance. After reconstitution each mL of suspension will contain 25 mg of azacitidine (100 mg/4 mL). The reconstituted product is a homogeneous, cloudy suspension, free of agglomerates. Discard the product if it contains large particles or agglomerates.

5. The rubber top should be cleaned and a new syringe with needle inserted. The vial should then be turned upside down; making sure the needle tip is below the level of the liquid. The plunger should then be pulled back to withdraw the amount of medicinal product required for the proper dose, making sure to purge any air trapped within the syringe. The syringe with needle should then be removed from the vial and the needle disposed of.

6. A fresh subcutaneous needle (recommended 25-gauge) should then be firmly attached to the syringe. The needle should not be purged prior to injection, in order to reduce the incidence of local injection site reactions.

7. If needed (doses over 100 mg) all the above steps for preparation of the suspension should be repeated. For doses greater than 100 mg (4 mL), the dose should be equally divided into 2 syringes (e.g., dose 150 mg = 6 mL, 2 syringes with 3 mL in each syringe).

8. The contents of the dosing syringe must be re suspended immediately prior to administration. The temperature of the suspension at the time of injection should be approximately 20°C to 25°C. To re suspend, vigorously roll the syringe between the palms until a uniform, cloudy suspension is achieved. Discard the product if it contains large particles or agglomerates.

The Reddy-Azacitidine suspension should be prepared immediately before use and the reconstituted suspension should be administered within 45 minutes. If elapsed time is greater than 45 minutes, the reconstituted suspension should be discarded appropriately and a new dose prepared. Alternatively, if the product needs to be reconstituted in advance of the administration, it must be placed in a refrigerator (2°C to 8°C) immediately after reconstitution, and kept in the refrigerator for a maximum of 8 hours. If the elapsed time in the refrigerator is greater than 8 hours, the suspension should be discarded appropriately and a new dose prepared. The syringe filled with reconstituted suspension should be allowed up to 30 minutes prior to administration to reach a temperature of approximately 20°C-25°C. If the elapsed time is longer than 30 minutes, the suspension should be discarded appropriately and a new dose prepared.

OVERDOSAGE

For management of a suspected drug overdose, contact your regional poison control centre.

One case of overdose with Azacitidine for injection was reported during clinical trials. A patient experienced diarrhea, nausea, and vomiting after receiving a single intravenous dose of approximately 290 mg/m^2, almost 4 times the recommended starting dose.

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 Reddy-Azacitidine overdose.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Azacitidine is believed to exert its antineoplastic effects by multiple mechanisms including cytotoxicity on abnormal hematopoietic cells in the bone marrow and hypomethylation of DNA. The cytotoxic effects of azacitidine may result from multiple mechanisms, including inhibition of DNA, RNA and protein synthesis, incorporation into RNA and DNA, and activation of DNA damage pathways. Non proliferating cells are relatively insensitive to azacitidine. Incorporation of azacitidine into DNA results in the inactivation of DNA methyltransferases, leading to hypomethylation of DNA. DNA hypomethylation of methylated genes may restore normal function to genes that are critical for differentiation and proliferation. The relative importance of DNA hypomethylation versus cytotoxicity or other activities of azacitidine to clinical outcomes has not been established.

Pharmacodynamics

As a pyrimidine nucleoside analogue designed to incorporate into RNA and DNA instead of cytidine, azacitidine has a broad spectrum of anti-metabolic effects. The primary pharmacodynamic effects of interest in the treatment of MDS are:

- Inhibition of DNA methylation
- Cytotoxicity by incorporation of azacitidine into DNA and RNA and inhibition of protein synthesis

Pharmacokinetics

Table 7 and text summarize SC and IV pharmacokinetic data conducted in one study of six MDS patients.

Table 7: Summary of Pharmacokinetic Parameters in Six MDS Patients

Dose	C_{max} (ng/mL)	t½ (min)	AUC	Clearance (L/hr)	Volume of distribution (L)
75 mg/m^2 single dose SC	750 ± 403	41 ± 8	961 ± 48	167 ± 49	Not Calculated
75 mg/m^2 single dose IV	2750 ± 1069	22 ± 1	1044 ± 286	147 ± 47	76 ± 26

Absorption: Following subcutaneous administration of a single 75 mg/m^2 dose, azacitidine was rapidly absorbed with peak plasma concentrations of 750 ± 403 ng/mL occurring at 0.5 h (the first sampling point) after dosing. The absolute bioavailability of azacitidine after subcutaneous relative to intravenous administration (single 75 mg/m^2 doses) was approximately 89 % based on area under the curve (AUC). AUC and C_{max} of subcutaneous administration of azacitidine were approximately dose proportional within the 25 to 100 mg/m^2 dose range. Multiple dosing at the recommended dose-regimen dose not result in drug accumulation.

Distribution: Following intravenous administration, the mean volume of distribution was 76 ± 26 liters, and systemic clearance was 147 ± 47 L/h.

Azacitidine Metabolism: Based on *in vitro* data, azacitidine metabolism does not appear to be mediated by cytochrome P450 isoenzymes (CYPs).

Metabolism of azacitidine is by spontaneous hydrolysis and by deamination mediated by cytidine deaminase. In human liver S9 fractions, formation of metabolites was independent of NADPH implying any metabolism would be catalysed by cytosolic enzymes.

Azacitidine Effect on CYP450 Isoenzymes: *In vitro* studies of azacitidine with cultured human hepatocytes indicate that at concentrations of 1.0 μM to 100 μM (i.e., up to approximately 30-fold higher than clinically achievable concentrations), azacitidine does not induce cytochrome P450 isoenzymes (CYPs) 1A2, 2C19, 3A4 or 3A5. In studies to assess inhibition of a series of P450 isoenzymes (CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4) incubated with 100 μM azacitidine, IC_{50} values could not be determined. Therefore, enzyme induction or inhibition by azacitidine at clinically achievable plasma concentrations is unlikely.

Excretion: Azacitidine is cleared rapidly from plasma with a mean elimination half life ($t_{1/2}$) after subcutaneous administration of 41 ± 8 minutes. Urinary excretion is the primary route of elimination of azacitidine and/or its metabolites. Following intravenous and subcutaneous administration of ^{14}C-azacitidine, 85 and 50% of the administered radioactivity was recovered in urine respectively, while < 1 % was recovered in feces.

Special Populations and Conditions

Pediatrics: No pharmacokinetic data are available in patients below the age of 18 years.

Geriatrics: In one pharmacokinetic study in six patients (see Table 7), six adult subjects received single intravenous and subcutaneous doses of Azacitidine for Injection. The mean ± standard deviation (SD) age of patients in this study was 71.0 ± 8.7 years (range 57 to 83 years).

Gender: The effects of gender on the pharmacokinetics of Azacitidine for Injection have not been studied.

Race: The effects of race on the pharmacokinetics of Azacitidine for Injection have not been studied.

Hepatic Insufficiency: The effects of hepatic insufficiency on the pharmacokinetics of Azacitidine for Injection have not been studied.

Renal Insufficiency: Severe renal impairment has no major effect on the pharmacokinetic exposure of azacitidine after single and multiple subcutaneous administrations. The pharmacokinetics of azacitidine were studied in adult cancer patients with normal renal function (n=6) or severe renal impairment (CL_{cr} < 30 mL/min/1.73 m^2; n=6). Following 5 consecutive days of SC administration of azacitidine at doses of 75 mg/m^2 mean azacitidine plasma concentrations versus time profiles were similar in shape, with higher concentrations observed in patients with severe renal impairment. Mean azacitidine AUC values measured on days 1 and 5 were increased approximately 70% and 40%, respectively, in patients with severe renal insufficiency compared to patients with normal renal function. Mean azacitidine C_{max} obtained from patients with severe renal impairment were increased approximately 42% and 6%, respectively, compared to patients with normal renal function on days 1 and 5.

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

STORAGE AND STABILITY

Storage

Store at room temperature (15 to 30°C).

Stability after reconstitution:

Chemical and physical in use stability of the reconstituted medicinal product has been demonstrated at 25°C for 45 minutes and at 2°C to 8°C for 8 hours.

From a microbiological point of view, the reconstituted product should be used immediately. If not used immediately, in use storage times and conditions prior to use are the responsibility of the user and must not be longer than 8 hours at 2°C to 8°C.

Incompatibilities

Reddy-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 Reddy-

Azacitidine and should therefore be avoided.

SPECIAL HANDLING INSTRUCTIONS

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

If reconstituted Reddy-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.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Reddy-Azacitidine is supplied in 100 mg single-use vials packaged in cartons of 1 vial. Each vial of Reddy-Azacitidine contains 100 mg of azacitidine and 100 mg mannitol as a sterile white lyophilized powder for reconstitution as a suspension for subcutaneous injection.

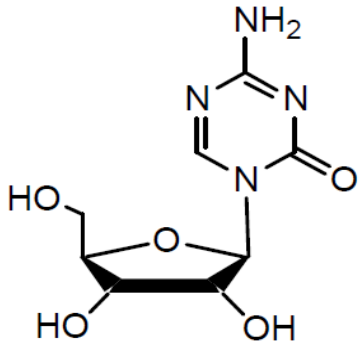
Packaging:

Reddy-Azacitidine is packed in type I flint tubular glass vial, stoppered with 20 mm bromobutyl and sealed with 20 mm violet flip off seal.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	azacitidine
Chemical name:	4-Amino-1-β-D-ribofuranosyl-*s*-triazin-2(1*H*)-one
Molecular formula and molecular mass:	$C_8H_{12}N_4O_5$ 244.20
Structural formula:	
Physicochemical properties:	Azacitidine is a white to off-white solid. Azacitidine was found to be insoluble in acetone, ethanol, and methyl ethyl ketone; slightly soluble in ethanol/water (50/50), sparingly soluble in water, water saturated octanol, 5% dextrose in water, N-methyl-2- pyrrolidone, normal saline and 5% Tween 80 in water; and soluble in dimethylsulfoxide (DMSO).

CLINICAL TRIALS

Phase 3 Pivotal International Open-Label Randomized Survival Study in Higher Risk MDS (AZA-001)

Study demographics and trial design

A prospective international, multicenter, controlled open label, randomized (1:1), parallel group Phase 3 comparative study was designed to determine whether Azacitidine for Injection resulted in improvement of survival in patients with primary MDS (AZA-001).

This pivotal study enrolled patients with an IPSS classification of Intermediate-2 (INT-2) or High primary MDS diagnosed as RAEB or RAEB-T according to the FAB classification. Under the current WHO classification system, RAEB-T patients (20-30 % blasts in the bone marrow) are now considered to be AML patients with 20% to 30% blasts and multi-lineage dysplasia. The primary endpoint of the study was overall survival.
Azacitidine for Injection was administered at a subcutaneous dose of 75 mg/m^2 daily for 7

days, followed by a rest period of 21 days (28-day treatment cycle) for a median of 9 cycles (range = 1-39 days). The median daily dose of Azacitidine for Injection was 75 mg/m^2, and the median cycle length was 34 days (i.e., the treatment cycle was extended by approximately 1 week based on the time of nadir and hematologic recovery).

Of the 358 patients enrolled in the study, 179 were randomized to receive Azacitidine for Injection plus best supportive care (BSC) and 179 were randomized to receive conventional care regimens (CCR) plus BSC (105 to BSC alone, 49 to low dose cytarabine and 25 to chemotherapy with cytarabine and anthracycline). Patients were pre selected by their physician to 1 of the 3 CCR prior to randomization.

The Azacitidine for Injection and CCR groups were comparable for baseline parameters (Table 8).

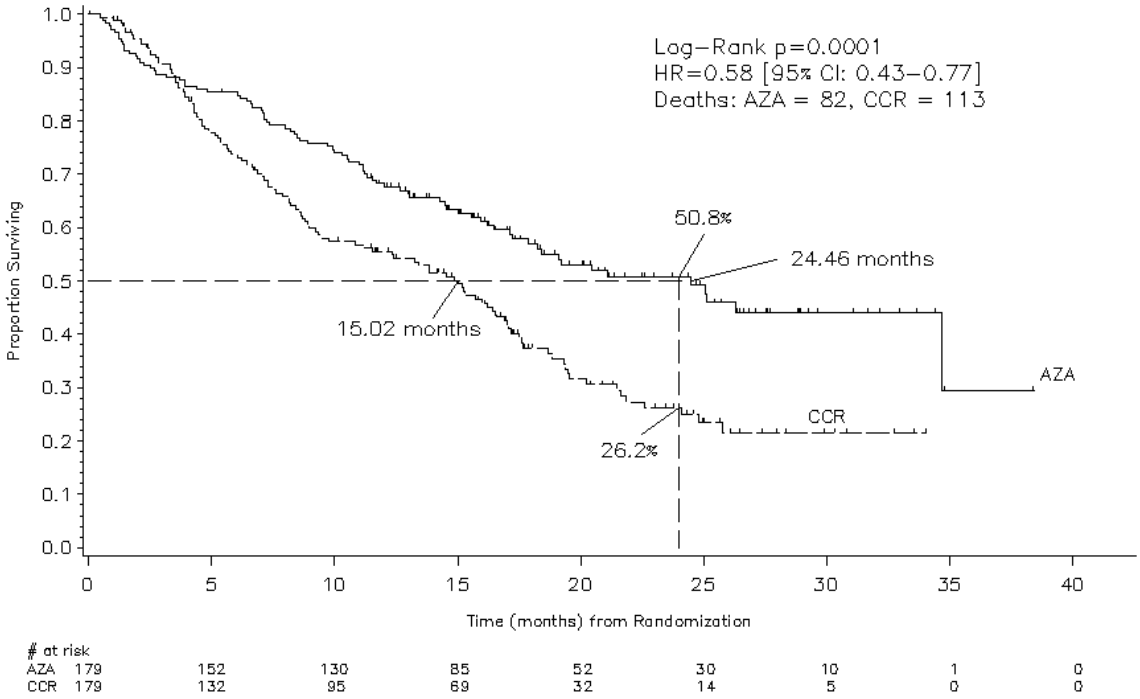
Table 8: AZA-001 Baseline Demographics and Disease Characteristics

Parameter	Azacitidine for Injection (N=179)	Combined CCR (N=179)
Gender – n (%)		
Male	132 (73.7)	119 (66.5)
Female	47 (26.3)	60 (33.5)
Race – n (%)		
Caucasian	177 (98.9)	175 (97.8)
Asian/Oriental	2 (1.1)	3 (1.7)
Hispanic	0 (0.0)	1 (0.6)
Age (years)		
Mean ± SD	68.0 ± 7.57	69.2 ± 7.87
Range	42 - 83	38 - 88
FAB Classification - n (%)		
RAEB	104 (58.1)	103 (57.5)
RAEB-T	61 (34.1)	62 (34.6)
mCMMoL	6 (3.4)	5 (2.8)
WHO Classification - n (%)		
RAEB-1	14 (7.8)	17 (9.5)
RAEB-2	98 (54.7)	95 (53.1)
CMMoL-1 and CMMoL-2	11 (6.2)	5 (2.8)
AML	55 (30.7)	58 (32.4)
Indeterminate	1 (0.6)	4 (2.2)
IPSS - n (%)		
INT-1 (0.5 to 1.0)	5 (2.8)	13 (7.3)
INT-2 (1.5 to 2.0)	76 (42.5)	70 (39.1)
High (≥ 2.5)	82 (45.8)	85 (47.5)
Transfusion product used in 56 days before randomization - n (%)		
Any transfusion product	115 (64.2)	117 (65.4)
Blood cells, packed human	111 (62.0)	114 (63.7)
Platelets	38 (21.2)	27 (15.1)

Study results

In the ITT analysis of 358 patients (179 Azacitidine for Injection and 179 CCR), Azacitidine for Injection treatment was associated with a median survival of 24.46 months *versus* 15.02 months for those receiving CCR treatment, a difference of 9.44 months, with a stratified log-rank p-value of 0.0001. The hazard ratio for the treatment effect was 0.58 (95 % CI: 0.43, 0.77). The two year survival rates were 50.8 % in patients receiving Azacitidine for Injection *versus* 26.2 % in patients receiving CCR ($p < 0.0001$).

Figure 1: Kaplan-Meier Curve of Time to Death from Any Cause: Intent-to Treat Population

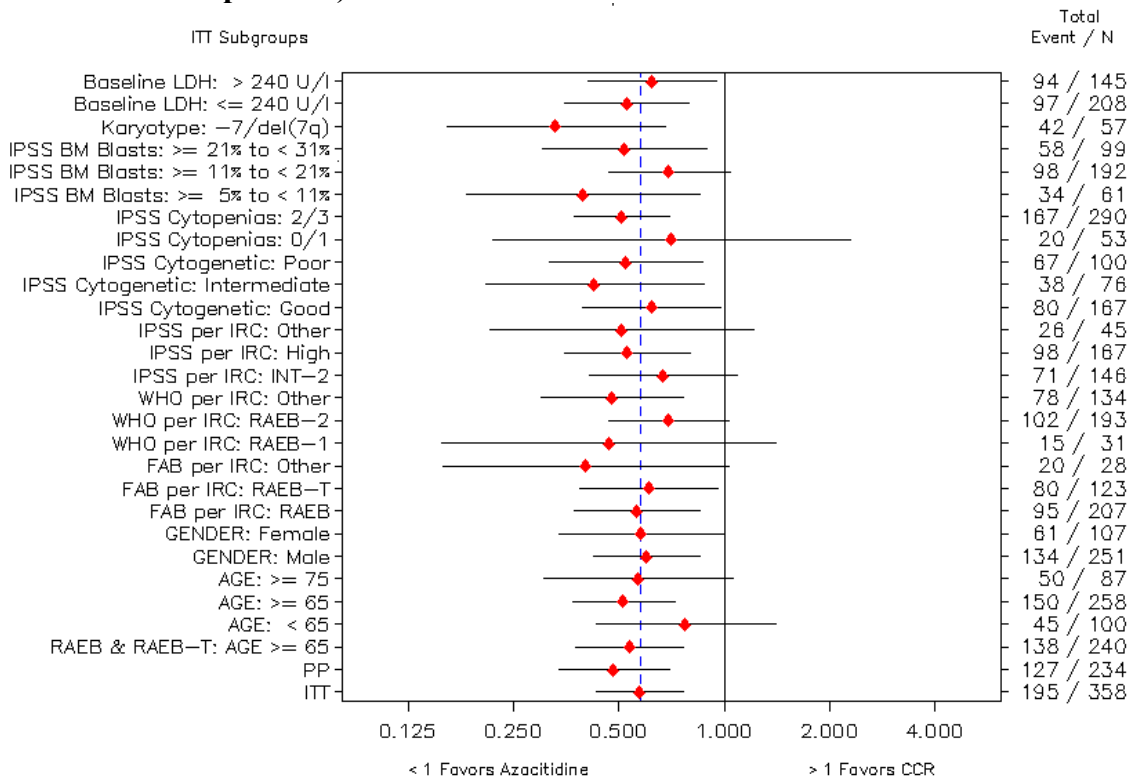


KEY: AZA=azacitidine (Azacitidine for Injection); CCR=conventional care regimens; CI=confidence interval; HR=hazard ratio

The survival benefits of Azacitidine for Injection were consistent regardless of the CCR treatment option (BSC alone, low dose cytarabine plus BSC or standard induction chemotherapy plus BSC) utilized in the control arm.

Figure 2 provides a graphical representation of hazard ratios and 95% CI for overall survival for the comparison of Azacitidine for Injection versus combined CCR by subgroup. The Azacitidine for Injection group had a reduced risk of death compared with patients in the combined CCR group for all subgroups. The intent-to-treat hazard ratio of 0.58 is captured within the confidence interval of all subgroups, which represents an overall consistency of the survival benefit within each subgroup.

Figure 2: Hazard Ratio and 95% Confidence Interval for Overall Survival by Subgroup for Azacitidine for Injection Versus Combined CCR (ITT Population)



When IPSS cytogenetic subgroups were analyzed, similar findings in terms of median overall survival were observed in all groups (good, intermediate, poor cytogenetics, including monosomy 7).

On analyses of age subgroups, an increase in median overall survival was observed for all groups (< 65 years, ≥ 65 years and ≥ 75 years).

Azacitidine for Injection treatment was associated with a median time to death or transformation to AML of 13.0 months versus 7.6 months for those receiving CCR treatment, an improvement of 5.4 months with a stratified log rank p value of 0.0025. Median time to AML transformation (measured from randomization to 30% bone marrow blasts or greater at last bone marrow assessment) was 17.8 months in the Azacitidine for Injection group compared with 11.5 months in the CCR group (hazard ratio, 0.50 [95% CI, 0.35 to 0.70], p<0.001).

Azacitidine for Injection treatment was also associated with a reduction in cytopenias, and their related symptoms. Azacitidine for Injection treatment led to a reduced need for red blood cell transfusions (see Table 9). In patients treated with Azacitidine for Injection who were RBC transfusion dependent at baseline and became transfusion independent, the median duration of RBC transfusion independence was 13.0 months.

Table 9: Effect of Azacitidine for Injection on RBC Transfusions in MDS Patients

Efficacy Parameter	Azacitidine for Injection plus BSC (n= 179)	Conventional Care Regimens (n= 179)
Number and percent of patients who were transfusion dependent at baseline who became transfusion independent on treatment[a]	50/111 (45.0%) (95% CI: 35.6%, 54.8%)	13/114 (11.4%) (95% CI: 6.2%, 18.7%)
Number and percent of patients who were transfusion-independent at baseline who became transfusion- dependent on treatment	10/68 (14.7%) (95% CI: 7.3%, 25.4%)	28/65 (43.1%) (95% CI: 30.9%, 56.0%)

[a] A patient was considered RBC transfusion independent during the treatment period if the patient had no RBC transfusions during any 56 consecutive days or more during the treatment period. Otherwise, the patient was considered transfusion dependent

Ad-hoc Analysis of Efficacy in WHO AML Patients in Study AZA-001

Demographics

The AZA-001 study used the FAB MDS classification for randomization. As the WHO classification of MDS became more widely accepted, the FAB entry diagnosis was reclassified by the IRC. According to the WHO classification, 113 out of 358 patients had entry diagnosis of AML with 20-30% blasts and multi-lineage dysplasia. These AML patients were randomly assigned to receive either Azacitidine for Injection (n=55) or CCR (n=58). The two groups (Azacitidine for Injection vs. CCR) were well balanced with respect to age (median, Min, Max): 70 (52, 80) and 70 (50, 83) years old; gender (M/F, %): 67.3/32.7 and 70.7/29.3; ECOG performance status (0/1/2): 29.1/63.6/7.3 and 37.9/58.6/0; IPSS (Int-2/High/Not applicable, %): 5.5/85.5/3.6 and 19.0/77.6/3.4, BM blasts (median, Min, Max, %): 23.0 (20, 34) and 23.1 (13.0, 68.9) and transfusion dependence (RBC/Platelet, %): 61.8/27.3 and 67.2/17.2. Overall, 24% of patients had unfavourable karyotype (-7/7q- or complex): Azacitidine for Injection 25% and CCR 22%; and 72% had an intermediate or good karyotype (Azacitidine for Injection 69% and CCR 74%). All AML patients had ≥ 1 cytopenia; 94% had multi- lineage dysplasia in both groups.

Results

In the subgroup analysis of the 113 patients (55 Azacitidine for Injection and 58 CCR) with 20-30% blasts and multilineage dysplasia classified as AML according to WHO classification, Azacitidine for Injection treatment was associated with a median survival of 24.5 months versus 16.0 months for those receiving CCR treatment, a difference of 8.5 months, with a stratified log-rank p-value of 0.0038. The hazard ratio for the treatment difference was 0.47 (95% CI: 0.28, 0.79). The two year survival rates were 50.2% in patients receiving Azacitidine

for Injection versus 15.9% in patients receiving CCR ($p < 0.0007$).

Of patients who were RBC transfusion dependent at baseline, 41.2% became RBC transfusion independent in the Azacitidine for Injection group, compared with 17.9% of the patients in the combined CCR group. The percentage of patients who were platelet transfusion dependent at baseline and became platelet transfusion independent during the treatment period was similar in the Azacitidine for Injection (53.3%) and combined CCR groups (40.0%).

The rate of infection requiring IV antibiotic, antifungal, or antiviral therapy was approximately 2-fold lower with Azacitidine for Injection compared to that of with CCR (0.58 vs.1.14 rate per patient-year). The relative risk of such infections was 0.51 (95% CI 0.29, 0.78; $p = 0.0029$) indicating a 49% risk reduction in the Azacitidine for Injection group relative to the CCR group.

In patients with one or more cytogenetic abnormalities at baseline, the percentage of patients with a major cytogenetic response was similar in the Azacitidine for Injection and combined CCR groups. Minor cytogenetic response was statistically significantly ($p = 0.0015$) higher in the Azacitidine for Injection group (34 %) compared with the combined CCR group (10 %).

DETAILED PHARMACOLOGY

Pharmacodynamics

The primary pharmacodynamic properties of azacitidine are hypomethylation of DNA and cytotoxicity of abnormal hematopoietic cells in the bone marrow.

Azacitidine inhibits the methylation of newly synthesized DNA by inhibiting DNA methyltransferase. Incorporation of azacitidine into the newly synthesized strand of DNA causes noncompetitive inhibition of DNA methyltransferase thus blocking the methylation of new DNA. It is widely recognized that hypermethylation of DNA can lead to the silencing of critical genes responsible for cell growth control and differentiation, and DNA hypomethylation of such genes may restore normal expression and function.

Treatment with azacitidine can induce cellular differentiation and is associated with DNA hypomethylation. Azacitidine-induced demethylation and differentiation frequently persist for many cell generations. In addition, hypermethylation of regions with dense CpG dinucleotides, referred to as CpG islands, spanning the promoter regions of tumor suppressor genes is commonly associated with cancers. The cause of aberrant hypermethylation of CpG islands is unclear but *de novo* methylation has been shown to increase with age. Overexpression of DNA methyltransferase may also contribute to hypermethylation of CpG islands. The relative importance of DNA hypomethylation versus cytotoxicity, or other activities of azacitidine, to clinical outcomes has not been established.

As an agent that incorporates into nucleic acids and alters gene expression, azacitidine also has the potential to cause harm. In addition to its role in DNA demethylation and cell differentiation, azacitidine has immunosuppressive, antimicrobial, mutagenic, embryotoxic, teratogenic, and tumorigenic effects.

Pharmacokinetics

After parenteral injection, both appearance and disappearance of the drug in blood occurs rapidly. Tissue distribution in mice following IP administered ^{14}C-azacitidine showed higher uptake of radioactivity in spleen and thymus than in organs such as kidney and liver. This finding may be due to a greater cell proliferation rate in lymphoid tissues than in other parenchymal organs. Cellular uptake of azacitidine is mediated by the facilitated nucleoside transport system. Metabolism of azacitidine is comparable to that of cytidine except that azacitidine is susceptible to spontaneous hydrolysis in neutral and alkaline solutions. Like cytidine, intracellular azacitidine is sequentially phosphorylated to form azacitidine triphosphate that may be incorporated into RNA or DNA. The first phosphorylation step, mediated by uridine-cytidine kinase, is rate limiting and subject to competitive inhibition by uridine triphosphate and cytidine triphosphate. Catabolism of azacitidine is mediated by cytidine deaminase to form 5-azauridine. Following IP treatment with ^{14}C-azacitidine in mice, recovery of radioactivity is primarily in the urine with a smaller amount eliminated in the feces.

TOXICOLOGY

Toxicology data were collected from *in vitro* studies and studies conducted in mice, rats, dogs, and rhesus monkeys. An overview of the principal toxicologic studies is provided in Table 10. The majority of the non-clinical safety information is derived from published scientific literature. These studies were not conducted according to current scientific / regulatory standards or guidelines.

Toxicity in animals, including effects on target organs (bone marrow, lymphoid tissues, liver and kidney), carcinogenicity, and severe reproductive toxicity occurred at administered dose levels in animals that are considerably lower than the intended clinical dose of 75 mg/m^2.

The relationship between observed toxicity and systemic exposure to azacitidine has not been well characterized in animals.

Table 10: Toxicology Program

Study Type and Duration	Route of Administration	Species or Test System	Results
Single-dose toxicity	PO, IP, and IV IV IV	Mouse Rat Dog	The lethal IV dose in 50% (LD50) of the animals after a single administration was approximately 117 mg/kg (351 mg/m^2) in mice and 51 mg/kg (306 mg/m^2) in rats. The approximate lethal dose in dogs was 13 mg/kg (266 mg/m^2).
Repeat-dose toxicity 5 days 5 days 5 days and 5 days in 2 cycles 2 days 14 days 14 days	 PO, IP, and IV IV IV PO PO IV	 Mouse Dog Dog Dog Dog Monkey	The animal models in toxicology were all more sensitive than humans to the toxicity of azacitidine. In the toxicology species, the main target organs were identified to be the bone marrow, liver, kidneys, and lymphoid tissue (spleen, lymph nodes).
Genotoxicity	*In vitro*	Salmonella typhimurium Escherichia coli Human lymphoblast cells Mouse lymphoma cells Hamster embryo cells	Azacitidine causes genotoxicity. Azacitidine is mutagenic and clastogenic in bacterial and mammalian cells.
Carcinogenicity 50 and 52 weeks 9 months	 IP IP	 Mouse Rat	Azacitidine has shown carcinogenic potential in mice and rats after IP administration.
Fertility	IP	Rat	Azacitidine has shown potential to produce adverse effects on male reproduction and fertility, including decreased testes and epididymides weights, decreased sperm counts, and decreased pregnancy rates.
Embryo Fetal Development	IP	Mouse Rat	Azacitidine produces dose-dependent embryotoxicity, embryolethality and teratogenicity in mice and rats after IP administration. Fetal malformations were noted at 0.3 mg/kg (1.8 mg/m^2) in rats and at 2 mg/kg (6 mg/m^2) in mice.

Single-dose studies in mice, rats, and dogs indicated that rodents are less sensitive than dogs to the acute effects of azacitidine. In rats, a lethal dose of approximately 51 mg/kg (306 mg/m^2) after IV administration was observed.

The main target organs of toxicity in animals after repeated administration are the bone marrow, liver, kidneys, and lymphoid tissues (spleen, lymph nodes, thymus). In a 14-day, repeat-dose PO study in dogs, dosing at 0.8 mg/kg/day (16 mg/m^2) was discontinued on day 10 due to morbidity. Findings consisted of mixed cell depletion in the bone marrow, lymphoid depletion in the thymus, spleen and lymph nodes, and centrilobular hepatocellular vacuolation in the liver. Dose-related findings were present at ≥ 0.2 mg/kg/day (≥ 4 mg/m^2/day). In monkeys administered 0.28 – 2.2 mg/kg/day (4.1 –32 mg/m^2) IV for 14 days, mortality was noted at the

high dose after 8 and 14 days. In these animals there were elevations of serum AST (SGOT), ALT (SGPT), and BUN.
Microscopically there was bone marrow hypoplasia, areas of necrosis and cloudy swelling of tubular epithelium in the kidneys, and cloudy swelling or fatty change in the liver. The NOAEL in monkeys was 0.28 mg/kg/day (4 mg/m^2).

An *in vivo* safety pharmacology study in dogs receiving azacitidine at single intravenous doses of ≥ 2 mg/kg reported increased heart rate, decreased blood pressure and increased QTc interval. The interpretations of this study are limited by concurrent confounding effects associated with toxicity including severe clinical signs (e.g., vomiting, flushed skin, decreased food consumption, and decreased spontaneous locomotor activity as well as fecal changes such as watery, mucous, or loose stool) in dogs. Additionally, large excursions in heart rate, decreases in potassium, and concurrent elevated autonomic nervous system tone as indicated by a spectrum of clinical signs and tachycardia limit the interpretation of the measurements. Results from *in vitro* tissue studies support the conclusion that azacitidine had no direct effects on vasodilatory parameters in the isolated rat aorta, no positive chronotropic effect was observed on the pacemaker activity of the guinea pig right atria, and there was no effect on heart rate and contractility in the isolated perfused guinea pig hearts; therefore, suggesting that blood pressure and heart rate changes in the cardiovascular dog study were also due to indirect effects of azacitidine.

Genotoxicity studies conducted *in vitro* have consistently shown that azacitidine is both mutagenic and clastogenic and induces chromosome aberrations *in vitro*. Azacitidine caused a mutagenic response in bacterial systems at 1-10 µg/plate, and induced an increased number of micronuclei in mammalian cells at 0.1 to 5 µM.

In fertility studies in male rats, azacitidine treatment resulted in reduced fertility after IP administration of 5 mg/kg (30 mg/m^2) 3 times per week for 11 weeks before mating. Males treated with 2.5 mg/kg (15 mg/m^2) were fertile but mating with untreated females resulted in increases in preimplantation embryo loss and increases in the average number of abnormal embryos.

In mice a 44% frequency of intrauterine embryonal death (increased absorption) were observed after a single intraperitoneal (IP) injection of 6mg/m^2 (approximately 8% of the recommended human dose on a mg/m^2 basis) of azacitidine on gestation day 10. Developmental abnormalities in the brain have been detected in mice given azacitidine on or before gestation day 15.

In rats, azacitidine was embryotoxic when given IP on gestation days 4-8 (postimplantation) at 6.0 mg/m^2 (1.0 mg/kg) although treatment during the preimplantation period (on gestation days 1-3) had no adverse effect on the embryos at this dose.

Azacitidine caused an increase in resorptions when administered as a single IP dose of ≥ 6.0 mg/m^2 (1.0 mg/kg) on gestation days 9 or 10. Statistically significant fetal anomalies were observed in rats following IP dosing of ≥ 1.8 mg/m^2 (0.3 mg/kg) on gestation day 1 to 8, or after a single IP dose of 3 to 12 mg/m^2 (0.5 to 2 mg/kg, respectively) on gestation day 9, 10, 11 or 12. Findings included: CNS anomalies (exencephaly/encephalocele), limb anomalies

(micromelia, club foot, syndactyly, oligodactyly) and others (microphthalmia, micrognathia, gastroschisis, oedema, and rib abnormalities). Doses in these studies ranged from 2.4 to 16% of the recommended human daily dose on a mg/m^2 basis.

Carcinogenicity studies have shown that azacitidine is a carcinogen in mice and rats after IP administration. In Sprague-Dawley rats administered 2.6 mg/kg (15.6 mg/m^2) and 5.2 mg/kg (31.2 mg/m^2) of azacitidine for approximately 9 months (34 weeks), neoplastic lesions were noted in multiple tissues.

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PART III: CONSUMER INFORMATION

[Pr] Reddy-Azacitidine
Azacitidine For Injection
100 mg/vial

This leaflet is part III of a three-part "Product Monograph" published when Reddy-Azacitidine was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Reddy-Azacitidine. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Reddy-Azacitidine is used in adults with either myelodysplastic syndrome (MDS) or Acute Myeloid Leukemia (AML) who are not eligible for stem cell transplantation. Both MDS and AML are blood disorders.

- In MDS, the bone marrow does not function and fails to produce enough healthy blood cells. You will only be given Reddy-Azacitidine if your form of MDS is considered "higher risk". Higher risk means that there is a danger that the disease will be fatal or that the patient could develop AML.
- AML is a type of cancer affecting the bone marrow, where blood cells develop. Blood cells that are not fully formed and do not work well are found in the blood.

What it does:
In patients with MDS and AML, Reddy-Azacitidine works by helping to correct the problem with the growth of immature cells in the bone marrow. Reddy-Azacitidine may also kill cells in bone marrow that have been reproducing abnormally.

When it should not be used:
Do not use Reddy-Azacitidine:

- If you are allergic to azacitidine or to any of the other ingredients of Reddy-Azacitidine
- If you have advanced liver cancer

What the medicinal ingredient is:
azacitidine

What the important nonmedicinal ingredients are:
Mannitol

What dosage forms it comes in:
Reddy-Azacitidine is supplied as a sterile freeze dried powder. After it is mixed with sterile water, it forms a suspension that can be injected subcutaneously (under the skin). Each vial contains 100 mg of azacitidine.

WARNINGS AND PRECAUTIONS

Reddy-Azacitidine should be prescribed and managed only by a doctor experienced in the use of anticancer drugs.

Reddy-Azacitidine can cause serious side effects:

- thrombocytopenia (abnormally small number of platelets in the blood);
- in rare cases, kidney failure, which can be life-threatening.

While taking Reddy-Azacitidine, you may receive supportive care to protect you from serious bleeding, anemia, infection, nausea and vomiting.

BEFORE you use Reddy-Azacitidine talk to your doctor or pharmacist if you:

- have low blood cell count (platelets, red or white blood cells)
- have kidney disease
- have liver disease
- have congestive heart failure
- are breastfeeding, pregnant or are planning to get pregnant

Reddy-Azacitidine may cause harm to an unborn baby. Females who could become pregnant should use effective contraception during treatment and up to 3 months after stopping treatment with Reddy-Azacitidine. Male patients should not father a child while receiving treatment with Reddy-Azacitidine and for 6 months after the last dose.

Reddy-Azacitidine may cause tumor lysis syndrome (metabolic abnormalities caused by the death of tumor cells), injection site necrosis (a serious condition due to the death of cells and tissue at the injection site), necrotizing fasciitis (a severe, life-threatening bacterial infection of the skin and soft tissue) and pyoderma gangrenosum (painful skin ulceration).

Reddy-Azacitidine is not recommended for use in children and adolescents below the age of 18.

INTERACTIONS WITH THIS MEDICATION

Interaction with other drugs is not known. You should tell your doctor or pharmacist about your other medicines including any that you bought without a prescription. These include vitamins and herbal products. While taking Reddy-Azacitidine, you should check with your doctor or pharmacist before taking any other medicines.

PROPER USE OF THIS MEDICATION

Your doctor will give you another medicine to prevent nausea and vomiting.

- Your doctor will choose your dose of Reddy-Azacitidine depending on your general condition, height and weight.
- Reddy-Azacitidine is given to you as an injection under the skin (subcutaneously) by a doctor or nurse. It may be given under the skin on your thigh, stomach or upper arm.

Usual dose:

- The usual dose is 75 mg per square meter of your body surface area.
- Your doctor will check your progress and may change your dose if necessary.
- Reddy-Azacitidine is given every day for 7 days in a row, followed by a rest period of 3 weeks. This "treatment cycle" will be repeated every 4 weeks. The treatment usually consists of at least 6 cycles.

Overdose:

If you think you have taken too much Reddy-Azacitidine, contact your healthcare professional hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

If you think that you have been given Reddy-Azacitidine more frequently than you should, or too high a dose, tell your healthcare provider immediately or contact your local poison control centre immediately.

Missed Dose:

If you think that you have missed a dose of Reddy-Azacitidine, tell your healthcare provider immediately.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Like all medicines, Reddy-Azacitidine can cause side effects. Side effects are usually more common during the first 2 cycles of treatment. They may be less common with further treatment.

Tell your doctor right away if you notice any of the following side effects:

- Fever - This may be due to an infection due to having a low white blood cell count.
- Chest pain or shortness of breath with or without fever - This may be due to an infection in your lungs called "pneumonia".
- Unexpected bleeding.
- Difficulty breathing, swelling of the lips, itching, or rash, which may be due to an allergic reaction.

Very common: Reduced red and/or white blood count; reduced platelet count; constipation; diarrhea; nausea; vomiting; pneumonia; chest pain; being short of breath; feeling tired; redness, pain or a skin reaction at the location where the needle enters your skin during injection; loss of appetite; joint aches; bruising; rash; red or purple spots under your skin; pain in your belly; itching; fever; sore nose and throat; dizziness; headache

Common: Bleeding inside your brain; blood infection; bone marrow failure leading to low red or white blood cell counts, or a low platelet count; low red and white blood cell counts, with a low platelet count occurring at the same time; urinary infection; cold sores (a viral infection); bleeding gums; bleeding in the stomach or gut; bleeding from hemorrhoids; bleeding in your eye; bleeding under your skin, or into your skin; blood in your urine; ulcers of your mouth or tongue; side effects where the needle went into your skin, including swelling, a hard lump, bruising, bleeding into your skin, rash, itching and/or changes in the color of the skin; redness of your skin; infection of the nose and throat, or sore throat; sore or runny nose or sinuses, low levels of potassium in your blood; high or low blood pressure; shortness of breath when you move; pain in your throat and voice box; indigestion; weight loss; lethargy; feeling generally unwell; muscle aches; anxiety or having trouble sleeping; being confused, hair loss

Uncommon: Allergic reaction

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptom / effect		Talk with your doctor or pharmacist		Stop taking drug and call your doctor or pharmacist
		Only if severe	In all cases	
Very Common	Fever / Infection or fever with low neutrophil count		✓	
Common	Feeling weak or tired with or without fever, unexpected bruises of any size, looking pale, chest pain, shortness of breath, palpitations / Blood system disorders		✓	
Common	Coughing, fever, with shortness of breath / Pneumonia		✓	
Common	Frequent need to urinate, pain or burning when you urinate, urine cloudy or smells bad, fever, chills / Urinary tract infection	✓		
Common	Nosebleed, bleeding from the eye or mouth	✓		
Common	Seizures, loss of consciousness, severe headache / Bleeding in the brain		✓	
Common	Blood in stool and urine		✓	
Uncommon	Allergic reaction		✓	

This is not a complete list of side effects. For any unexpected effects while taking Reddy-Azacitidine, contact your doctor or pharmacist.

HOW TO STORE IT

Store at room temperature (15 to 30°C). Keep out of reach of children.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

MORE INFORMATION

If you want more information about [Pr] **Reddy-Azacitidine:**
Talk to your healthcare professional.
Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website at **http://hc-sc.gc.ca/index-eng.php**; the manufacturer's website **www.drreddys.com**, or by calling **1-855-845-1739**
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DIN Owner:
Dr. Reddy's Laboratories Limited
Bachupally – 500 090 INDIA
1-855-845-1739
druginfo@drreddys.com
Canadian Importer by:
Dr. Reddy's Laboratories Canada Inc.,
2425 Matheson Blvd East, #754
Mississauga, ON L4W 5K4 CANADA
This leaflet is prepared by Dr. Reddy's Laboratories Limited.

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