

NEW ZEALAND DATA SHEET

1 PRODUCT NAME

Azacitidine - Dr Reddy's

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Azacitidine 100 mg Powder for Injection

3 PHARMACEUTICAL FORM

Each vial contains 100 mg azacitidine and 100 mg mannitol.

Azacitidine - Dr Reddy's is supplied in a colourless single use Type I glass vial sealed with butyl rubber stopper and aluminium seal with plastic button.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Azacitidine - Dr Reddy's is indicated for the treatment of patients with:

- Intermediate-2 and High-risk Myelodysplastic Syndromes (MDS) according to the International Prognostic Scoring System (IPSS),
- Chronic Myelomonocytic Leukemia (CMML) [10%-29% marrow blasts without Myeloproliferative Disorder],
- Acute Myeloid Leukemia (AML) with 20-30% blasts and multi-lineage dysplasia, according to World Health Organisation Classification (WHO), in whom allogenic stem cell transplantation is not indicated.

4.2 Dose and method of administration

Azacitidine - Dr Reddy's treatment should only be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Patients should be pre-medicated for nausea and vomiting.

Recommended Dosage in Adults:

First Treatment Cycle

The recommended starting dose for the first treatment cycle, for all patients regardless of baseline haematology laboratory values, is 75 mg/m² of body surface area given subcutaneously or by intravenous infusion, daily for seven days, followed by a rest period of 21 days (28-day treatment cycle).

Subsequent Treatment Cycles

Cycles should be repeated every 28 days. It is recommended that patients be treated for a minimum of 6 cycles. However, complete or partial response may require more than 6 treatment cycles. Treatment may be continued as long as the patient continues to benefit or until disease progression.

Patients should be monitored for haematological response and renal toxicities, and a dose delay or reduction as described below may be necessary.

With subcutaneous injection, rotate sites for injection (thigh, abdomen, or upper arm). New injections should be given at least 2.5 cm or one inch from the previous site and never into areas where the site is tender, bruised, red, or hard.

Dosage Adjustment based on Haematology Laboratory Values:

Patients without reduced baseline blood counts (i.e. WBC $\geq 3.0 \times 10^9/L$ and ANC $\geq 1.5 \times 10^9/L$, and platelets $\geq 75.0 \times 10^9/L$) prior to the first treatment

If haematological toxicity is observed following Azacitidine - Dr Reddy's treatment (as defined by: Platelets $< 50.0 \times 10^9/L$ and/or ANC $< 1 \times 10^9/L$), the next cycle of Azacitidine - Dr Reddy's 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. If recovery has not been achieved within 14 days, the dose should be reduced according to the following table. Following dose modifications, the cycle duration should return to 28 days.

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

*Recovery = counts \geq Nadir Count + (0.5 x [Baseline Count – Nadir Count])

Patients with reduced baseline blood counts (i.e. WBC $< 3.0 \times 10^9/L$, ANC $< 1.5 \times 10^9/L$, or platelets $< 75.0 \times 10^9/L$) prior to the first 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 Azacitidine - Dr Reddy's therapy should be delayed until the platelet count and the ANC have recovered {counts \geq Nadir Count + (0.5 x [Baseline Count – Nadir Count])} and, if recovery has not been achieved within 14 days, bone marrow cellularity must be determined. If the bone marrow cellularity is $> 50\%$ no dose adjustments should be made. If bone marrow cellularity is $\leq 50\%$, delay treatment and reduce the dose according to the following table:

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

*Recovery = counts \geq Nadir Count + (0.5 x [Baseline Count – Nadir Count])

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

Dose adjustment based on renal function and serum electrolytes:

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. Similarly, if unexplained and clinically significant elevations of serum creatinine or blood urea nitrogen (BUN) occur, the next cycle should be delayed until values return to normal or baseline and the dose should be reduced by 50% on the next treatment cycle (see Warnings and Precautions).

Preparation of Azacitidine - Dr Reddy's:

Azacitidine - Dr Reddy's is a cytotoxic drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing Azacitidine - Dr Reddy's suspensions. Procedures for proper handling and disposal of anticancer drugs should be applied.

If reconstituted Azacitidine - Dr Reddy's 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.

The Azacitidine - Dr Reddy's vial is single-use and does not contain any preservatives. Unused portions of each vial should be discarded in accordance with local requirements for disposal of cytotoxic compounds.

Instructions for Subcutaneous Administration:

Azacitidine - Dr Reddy's must be reconstituted with water for injections to form a uniform suspension prior to administration as follows. Aseptically add 4 mL of sterilised water for injections slowly into the vial. Vigorously shake the vial until a uniform, cloudy suspension is achieved. No filters, and no adaptors, spikes or closed systems that contain filters, should be used after reconstitution since these could remove the active substance. The suspension contains azacitidine 25 mg/mL. The maximum recovery of azacitidine is 96% per vial following reconstitution.

Suspension stability

To reduce microbiological hazard, use as soon as practicable after reconstitution.

Reconstituted Azacitidine - Dr Reddy's suspension may be stored for up to:

- 1 hour at 25°C, or
- 8 hours between 2°C and 8°C, or
 - 22 hours between 2°C and 8°C when reconstituted with refrigerated (2°C-8°C) water for injections.

Preparation for Immediate Subcutaneous Administration: Doses greater than 4 mL should be divided equally into two syringes and injected into two separate sites. The product may be held at room temperature (25°C) 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. Doses greater than 4 mL should be divided equally into two syringes. The product must be refrigerated immediately.

- When Azacitidine - Dr Reddy's is reconstituted using water for injections that has not been refrigerated, the product may be held under refrigerated conditions (2°C-8°C) for up to 8 hours.
- When Azacitidine - Dr Reddy's is reconstituted using refrigerated (2°C-8°C) water for injections, the product may be stored under refrigerated conditions (2°C-8°C) for up to 22 hours.

After removal from refrigerated conditions, the suspension may be allowed to equilibrate to room temperature for up to 30 minutes prior to administration.

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.

Doses greater than 4 mL should be divided equally into 2 syringes and injected into 2 separate sites. Rotate sites for each injection (thigh, abdomen, or upper arm). New injections should be given at least 2.5 cm or one inch from an old site and never into areas where the site is tender, bruised, red, or hard.

Instructions for Intravenous Administration:

Preparation for intravenous administration

Reconstitute the appropriate number of Azacitidine - Dr Reddy's vials to achieve the desired dose as follows:

Reconstitute each vial with 10 mL sterile water for injection. Vigorously shake or roll the vial until all solids are dissolved. The resulting solution will contain azacitidine 10 mg/mL. The solution should be clear. Do not filter the solution as this could remove any undissolved active substance.

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

Intravenous Solution Incompatibility

Azacitidine - Dr Reddy's is incompatible with 5% dextrose solution, volulyte or solutions that contain bicarbonate. These solutions have the potential to increase the rate of degradation of Azacitidine - Dr Reddy's and should therefore be avoided.

Intravenous Administration:

Azacitidine - Dr Reddy's solution is administered as an intravenous infusion. Administer the total dose over a period of 10-40 minutes. The intravenous administration must be completed within 45 minutes of reconstitution of the Azacitidine - Dr Reddy's vial.

4.3 Contraindications

Azacitidine - Dr Reddy's is contraindicated in the following patients:

- patients with known hypersensitivity to azacitidine or to any of the excipients
- patients with advanced malignant hepatic tumours (see Warnings and Precautions)
- pregnancy
- patients with severe renal impairment (creatinine clearance < 30 mLs/min).

4.4 Special warnings and precautions for use

Paediatric use

The safety and efficacy of azacitidine in children and adolescents under 18 years of age has not been established.

Use in the elderly

No specific dose adjustments are recommended for the elderly. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function.

Genotoxicity

Azacitidine was mutagenic, as assessed in *Salmonella typhimurium*, L5178Y mouse lymphoma cells and human lymphoblast TK6 cells. Azacitidine was clastogenic in the *in vitro* micronucleus assays in Syrian hamster embryo fibroblasts and L5178Y mouse lymphoma cells. Azacitidine induced morphological transformation in Syrian hamster kidney and embryo fibroblasts. No *in vivo* tests have been conducted with azacitidine.

Carcinogenicity

Azacitidine has been shown to be carcinogenic when administered by the intraperitoneal route 2 or 3 times weekly for 50-52 weeks in mice at doses of 7-13 mg/m² and for 8-36 weeks in rats at doses of 16-60 mg/m². These doses are well below the recommended human daily dose (when compared on a mg/m² basis). Tumour types included lung, testicular, mammary gland, and skin tumours, lymphomas and tumours of the haematopoietic system.

Haematology

Treatment with Azacitidine - Dr Reddy's is associated with anaemia, neutropenia and thrombocytopenia, particularly during the first 2 cycles. Complete blood counts should be performed as needed to monitor response and toxicity, but at a minimum, prior to each dosing cycle. After administration of the recommended dose for the first cycle, in the presence of cytopenias, the dose for subsequent cycles should be reduced or delayed based on nadir counts and haematologic response as described in Dosage and Administration.

Use in Patients with Hepatic Impairment

No formal studies have been conducted in patients with hepatic impairment (see Pharmacokinetics). The pivotal safety and efficacy study excluded patients with bilirubin > 1.5 times the upper limit of normal, or with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.0 times the upper limit of normal. The safety of azacitidine in such patients has therefore not been established.

Patients with extensive tumour burden due to metastatic disease have been rarely reported to experience progressive hepatic coma and death during azacitidine treatment, especially in such patients with baseline serum albumin < 30 g/L. Azacitidine is contraindicated in patients with advanced malignant hepatic tumours (see Contraindications).

Renal Toxicity and Use in Patients with Renal Impairment

Renal abnormalities ranging from elevated serum creatinine to renal failure and death were reported rarely in patients treated with intravenous (IV) azacitidine in combination with other chemotherapeutic agents. In addition, renal tubular acidosis, defined as a fall in serum bicarbonate to < 20 mmol/L in association with an alkaline urine and hypokalaemia (serum potassium < 3 mmol/L) developed in 5 subjects with chronic myelogenous leukemia (CML) treated with azacitidine and etoposide. If unexplained reductions in serum bicarbonate (< 20 mmol/L) or elevations of serum creatinine or BUN occur, the dose should be reduced or delayed as described in Dosage and Administration.

No formal studies have been conducted in patients with renal impairment. Since azacitidine and/or its metabolites are primarily excreted by the kidneys, patients with mild or moderate renal impairment should be monitored closely and the dose adjusted based on haematology and renal laboratory values (see Dosage and Administration). There are inadequate pharmacokinetic or safety data to support the use of azacitidine in patients with severe renal impairment (creatinine clearance < 30 mLs/min – see Contraindications).

Patients should be advised to report oliguria and anuria to the healthcare provider immediately.

Cardiac and pulmonary disease

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 in these patients has not been established.

Tumour Lysis Syndrome

The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

Laboratory Tests

Liver function tests, serum creatinine and serum bicarbonate should be determined prior to initiation of therapy and prior to each treatment cycle.

Complete blood counts should be performed as needed to monitor response and toxicity, but at a minimum, prior to each treatment cycle.

4.6 Fertility, pregnancy and lactation

Use in male patients

Men should be advised not to father a child while receiving treatment. Contraceptive measures are recommended. Before starting treatment, men are advised to seek counselling on sperm storage. Female partners of male patients receiving azacitidine should not become pregnant (see Effects on Fertility).

Effects on Fertility

Azacitidine had adverse effects on male fertility in rodents. Administration of azacitidine to male mice at 9.9 mg/m² IP (well below the recommended human daily dose on a mg/m² basis) daily for 3 days prior to mating with untreated female mice resulted in decreased fertility and increased pre- and post-implantation loss. Treatment of male rats three times per week for 6-11 weeks at doses well below the recommended human daily dose on a mg/m² basis, resulted in decreased weight of the testes and epididymides, decreased sperm counts accompanied by decreased pregnancy rates and increased loss of embryos in mated females, and an increase in abnormal embryos in mated females when examined on day 2 of gestation (see Use in male patients). There have been no animal studies which have examined the effects of azacitidine on female fertility.

Use in Pregnancy

There are no adequate data on the use of azacitidine in pregnant women. Studies in animals have shown reproductive toxicity including teratogenic effects at relatively low doses. Azacitidine must not be used during pregnancy.

Increased foetal resorptions were observed in mice treated with azacitidine (6 mg/m² IP, well below the recommended human daily dose) on single days during gestation (days 10-14). In pregnant rats given azacitidine on gestation days 4-8 at doses well below the recommended human dose, foetal survival and foetal weights were decreased.

Azacitidine caused multiple foetal abnormalities in rats after administration of a single IP dose of 3 to 12 mg/m² (well below the recommended human daily dose) on gestation day 9, 10, 11 or 12.

Foetal abnormalities included CNS abnormalities (exencephaly/encephalocele), limb abnormalities (micromelia, club foot, syndactyly, oligodactyly) and others (microphthalmia, micrognathia, gastroschisis, oedema, and rib abnormalities). Azacitidine also caused multiple foetal abnormalities in mice after administration of a single IP dose of 6 mg/m² (well below the recommended human daily dose) on gestation day 10, 11 or 12. Foetal abnormalities included: CNS abnormalities (exencephaly), limb abnormalities (malformed limbs, polydactyly, syndactyly, oligodactyly) and others (cleft palate, skull bone defects and rib abnormalities).

Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with azacitidine. If a patient becomes pregnant while taking this drug, the patient should be appraised for the potential hazard to the foetus (see Contraindications).

Men and women of childbearing potential must use effective contraception during and up to 3 months after treatment.

Use in Lactation

It is not known whether azacitidine or its metabolites are excreted in human milk. The safety of azacitidine has not been investigated in lactating animals. Given the serious toxicity (severe target organ toxicity, genotoxicity and carcinogenicity) observed in other animal studies and the potential for serious adverse effects on the nursing child, breastfeeding must be discontinued during azacitidine therapy.

4.5 Interaction with other medicines and other forms of interaction

No formal clinical drug interaction studies with azacitidine have been conducted. It is not known whether azacitidine metabolism is affected by microsomal enzyme inhibitors or inducers. Concomitant administration of medications known to be strong metabolising enzyme inducers or inhibitors is not recommended. Where such medications are considered essential, alternatives that are not strong inducers or inhibitors of metabolising enzymes should be sought.

4.7 Effects on ability to drive and use machines

While no studies on the effects of azacitidine on the ability to drive and use machines have been performed, patients should be advised that they may experience undesirable effects such as dizziness during treatment. Therefore caution should be recommended when driving a car or operating machinery.

4.8 Undesirable effects

The most commonly reported adverse events with azacitidine treatment were haematological (thrombocytopenia, neutropenia and leukopenia [usually Grade 3-4], and anaemia [usually Grade 1-2]), or those associated with administration (nausea, vomiting and injection site reactions, usually Grade 1-2). Adverse reactions associated with intravenously administered azacitidine were similar in frequency and severity compared with subcutaneously administered azacitidine. This assessment was mostly based on cross-study comparisons, with studies of differing design (including considerably longer IV infusion of azacitidine than is now recommended) and differing patient populations. The most common adverse reactions by IV route also included petechiae, rigors, weakness and hypokalemia.

The following Table 1 shows the adverse events that occurred at a frequency of greater than or equal to 10% in the azacitidine group in the pivotal clinical study.

Table 1: Most frequently reported adverse events (≥ 10% in the azacitidine treatment arm) from the pivotal clinical study (AZA PH GL 2003 CL 001 – subcutaneous route of administration)

System Organ Class Preferred Term	Number (%) of Patients			
	Azacitidine (N = 175)		BSC (N = 102)	
	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Blood and lymphatic system disorders				
Thrombocytopenia	122 (69.7)	102 (58.3)	35 (34.3)	29 (28.4)
Neutropenia	115 (65.7)	107 (61.1)	29 (28.4)	22 (21.6)
Anaemia	90 (51.4)	24 (13.7)	45 (44.1)	9 (8.8)
Leukopenia	32 (18.3)	26 (14.9)	2 (2.0)	1 (1.0)
Febrile Neutropenia	24 (13.7)	22 (12.6)	10 (9.8)	7 (6.0)
Gastrointestinal Disorders				
Constipation	88 (50.3)	2 (1.1)	8 (7.8)	0
Nausea	84 (48.0)	3 (1.7)	12 (11.8)	0
Vomiting	47 (26.9)	0	7 (6.9)	0
Diarrhoea	38 (21.7)	1 (0.6)	18 (17.6)	1 (1.0)
Abdominal Pain	22 (12.6)	7 (4.0)	7 (6.9)	0
General Disorders and Administration Site Conditions				
Injection/catheter site erythema	75 (42.9)	0	0	0
Pyrexia	53 (30.3)	8 (4.6)	18 (17.6)	1 (1.0)
Injection site reaction	51 (29.1)	1 (0.6)	0	0
Fatigue	42 (24.0)	6 (3.4)	12 (11.8)	2 (2.0)
Injection site pain	33 (18.9)	0	0	0
Asthenia	28 (16.0)	4 (2.3)	15 (14.7)	2 (2.0)
Oedema Peripheral	23 (13.1)	0	13 (12.7)	0
Infections and infestations				
Nasopharyngitis	33 (18.9)	2 (1.1)	13 (12.7)	0
Pneumonia	22 (12.6)	18 (10.3)	12 (11.8)	8 (7.8)
Bronchitis	17 (9.7)	0	8 (7.8)	0
Injury, poisoning and procedural complications				
Transfusion reaction	21 (12.0)	4 (2.3)	5 (4.9)	1 (1.0)
Metabolism and nutrition disorders				
Anorexia	25 (14.3)	3 (1.7)	9 (8.8)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)				
Acute myeloid leukaemia	30 (17.1)	28 (16.0)	36 (35.3)	32 (31.4)
Nervous system disorders				
Headache	25 (14.3)	0	8 (7.8)	0
Dizziness	17 (9.7)	1 (0.6)	7 (6.9)	0

Respiratory, Thoracic and mediastinal disorders				
Cough	34 (19.4)	1 (0.6)	15 (14.7)	0
Epistaxis	29 (16.6)	9 (5.1)	16 (15.7)	7 (6.9)
Dyspnoea	26 (14.9)	6 (3.4)	5 (4.9)	2 (2.0)
Skin and subcutaneous tissue disorders				
Pruritus	21 (12.0)	0	2 (2.0)	0
Petechiae	20 (11.4)	2 (1.1)	4 (3.9)	0
Rash	18 (10.3)	0	1 (1.0)	0
Vascular disorders				
Haematoma	21 (12.0)	0	10 (9.8)	0

Multiple reports of the same preferred term for a patient are counted only once within each treatment group. Preferred terms were coded using the MedDRA Version 10.0. The severity of the adverse events is graded according to NCI CTC Version 2.0. Grade 3 = severe; Grade 4 = life threatening.
BSC = Best supportive care.

The adverse reactions for which a causal relationship with azacitidine treatment could reasonably be established are listed below. Frequencies given are based on the observations during the pivotal clinical study or two supporting clinical studies.

Frequencies are defined as: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $< 1/100$). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Adverse Drug Reactions (ADRs) observed in patients treated with azacitidine:

Infections and infestations

Very Common: pneumonia, nasopharyngitis

Common: neutropenic sepsis, upper respiratory tract infection, urinary tract infection, sinusitis, pharyngitis, rhinitis, herpes simplex

Blood and lymphatic system disorders

Very Common: febrile neutropenia, neutropenia, leukopenia, thrombocytopenia, anaemia

Common: bone marrow failure, pancytopenia

Immune system disorders

Uncommon: hypersensitivity reactions

Metabolism and nutrition disorders

Very Common: anorexia

Common: hypokalemia

Psychiatric disorders

Common: confusional state, anxiety, insomnia

Nervous system disorders

Very Common: dizziness, headache

Common: intracranial haemorrhage, lethargy

Eye disorders

Common: eye haemorrhage, conjunctival haemorrhage

Vascular disorders

Common: hypertension, hypotension, haematoma

Respiratory, thoracic and mediastinal disorders

Very Common: dyspnoea

Common: dyspnoea exertional, pharyngolaryngeal pain

Gastrointestinal disorders

Very Common: diarrhoea, vomiting, constipation, nausea, abdominal pain

Common: gastrointestinal haemorrhage, haemorrhoidal haemorrhage, stomatitis, gingival bleeding, dyspepsia

Skin and subcutaneous tissue disorders

Very Common: petechiae, pruritus, rash, ecchymosis

Common: purpura, alopecia, erythema, rash macular

Musculoskeletal and connective tissue disorders

Very Common: arthralgia

Common: myalgia, musculoskeletal pain

Renal and urinary disorders

Common: haematuria

General disorders and administration site conditions

Very Common: fatigue, pyrexia, chest pain, injection site erythema, injection site pain, injection site reaction (unspecified)

Common: injection site: bruising, haematoma, induration, rash, pruritus, inflammation, discoloration, nodule and haemorrhage, malaise

Investigations

Common: weight decreased

Haematologic Events

The most commonly reported adverse events associated with azacitidine treatment were haematological including: thrombocytopenia, neutropenia and leukopenia (usually Grade 3 or 4), and anaemia (usually Grade 1 or 2). There is a greater risk of these events occurring during the first 2 cycles, after which they occur with less frequency in patients with restoration of haematological function. Most haematological adverse reactions were managed by routine monitoring of complete blood counts and delaying azacitidine administration in the next cycle. Blood transfusions were provided for anaemia or thrombocytopenia and prophylactic antibiotics and/or growth factor support for neutropenia as required.

Thrombocytopenia may lead to bleeding and patients should be monitored for signs and symptoms of bleeding, particularly those with pre-existing or treatment-related thrombocytopenia. Infections as a result of neutropenia may be managed with the use of anti-infectives plus growth factor support (e.g. G-CSF).

Hypersensitivity

Serious hypersensitivity reactions (0.25%) have been reported in patients receiving azacitidine. In case of an anaphylactic-like reaction, treatment with azacitidine should be immediately discontinued and appropriate symptomatic treatment initiated.

Skin and Subcutaneous Tissue Adverse Reactions

The majority of skin and subcutaneous adverse reactions were associated with the injection site. None of these adverse reactions led to temporary or permanent discontinuation of azacitidine, or reduction of azacitidine dose in the pivotal study. The majority of adverse reactions occurred during the first 2 cycles and tended to decrease with subsequent cycles. Subcutaneous adverse reactions such as injection site rash, inflammation, pruritus, erythema and skin lesion may require management with concomitant medicinal products, such as antihistamines, corticosteroids and non-steroidal anti inflammatory drugs (NSAIDs).

Gastrointestinal Adverse Reactions

The most commonly reported gastrointestinal adverse reactions associated with azacitidine treatment included constipation, diarrhoea, nausea and vomiting. These adverse reactions were managed symptomatically with anti-emetics for nausea and vomiting, antidiarrhoeals for diarrhoea, and laxatives and/or stool softeners for constipation.

Renal adverse reactions

Renal abnormalities, ranging from elevated serum creatinine to renal tubular acidosis, renal failure and death were reported rarely in patients treated with azacitidine (see Warnings and Precautions).

Hepatic adverse reactions

Patients with extensive tumour burden due to metastatic disease have been rarely reported to experience progressive hepatic coma and death during azacitidine treatment (see Warnings and Precautions).

Post-marketing Data

The following events have been reported in the post-marketing setting:

- Interstitial lung disease
- Tumour Lysis Syndrome
- Injection Site Necrosis
- Cellulitis
- Necrotizing fasciitis
- Acute febrile neutrophilic dermatosis
- Pyoderma gangrenosum.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

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 overdosage. In New Zealand, contact the National Poison Centre on 0800 POISON or 0800 764 766 for advice on management.

One case of overdose with azacitidine was reported during clinical trials. A patient experienced diarrhoea, nausea, and vomiting after receiving a single IV 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Description

Azacitidine is a white to off-white solid. It is insoluble in acetone, ethanol, and methyl ethyl ketone. Azacitidine is slightly soluble in ethanol/water (50/50) and propylene glycol; it is sparingly soluble in water (13.8 mg/mL, 5% glucose in water and in normal saline).

Approved Name: azacitidine

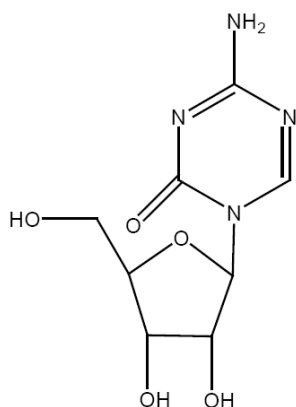
Molecular formula: C₈H₁₂N₄O₅

Molecular weight: 244

The CAS number: 320-67-2

Chemical name: 4-amino-1-β-D-ribofuranosyl-s-triazin-2(1H)-one.

Chemical structure:



Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, antimetabolites, pyrimidine analogues, ATC code: *L01BC07*

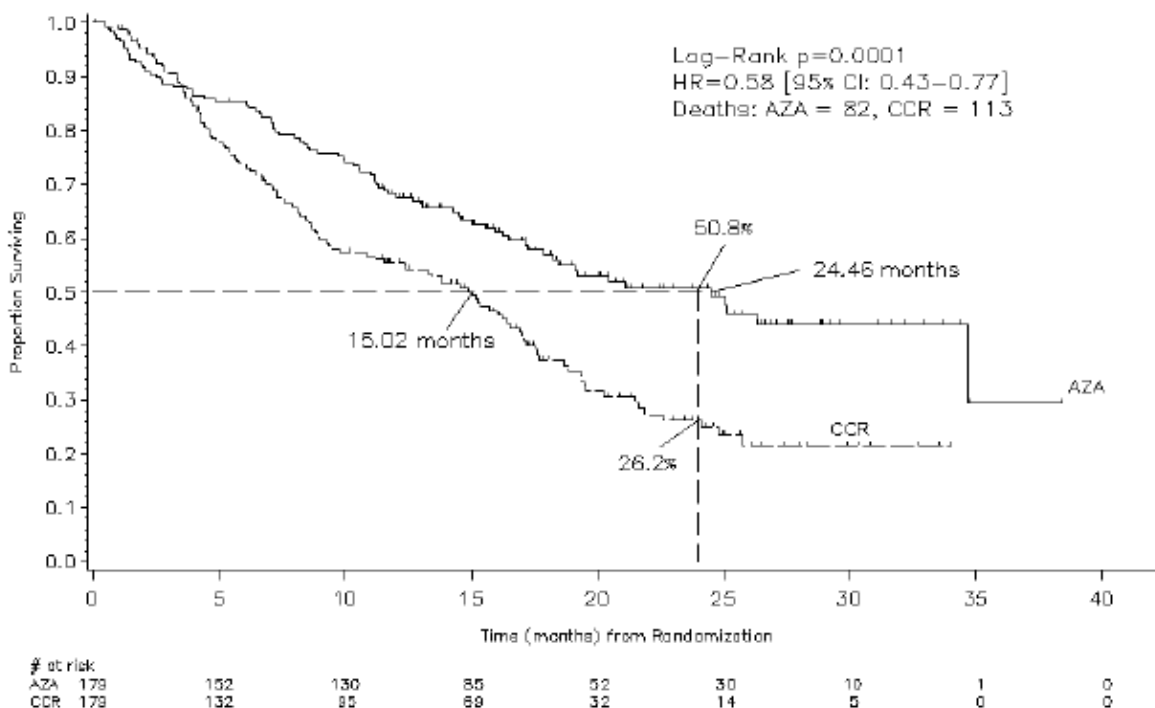
Azacitidine is believed to exert its antineoplastic effects by causing hypomethylation of DNA and direct cytotoxicity on abnormal haematopoietic cells in the bone marrow. DNA hypomethylation may allow for the re-expression of genes involved in normal cell cycle regulation and differentiation. The cytotoxic effects of azacitidine may be due in part to its incorporation into RNA

with subsequent inhibition of protein synthesis and/or its ability to activate DNA damage pathways leading to apoptosis. *In vitro*, non-proliferating cells are relatively insensitive to azacitidine.

Clinical Studies

The efficacy and safety of azacitidine were demonstrated in an international, multicenter, controlled, open-label, randomized, parallel-group, Phase 3 comparative study (AZA-PH-GL 2003-CL 001) in patients with: Intermediate-2 and High-risk MDS according to IPSS, RAEB, RAEB-T and mCMML according to the French American British (FAB) classification system. RAEB-T patients (21-30% blasts) are now considered to be AML under the WHO classification system. Azacitidine plus Best Supportive Care (BSC) was compared to Conventional Care Regimens (CCR). CCR consisted of BSC (n = 105), Low-Dose Cytarabine plus BSC (n = 49) or Standard Induction Chemotherapy plus BSC (n = 25). Patients were pre-selected (by their physician) to 1 of the 3 CCR prior to randomization. Patients received this pre-selected regimen if not randomized to azacitidine. The primary endpoint of the study was overall survival. Azacitidine was administered at a subcutaneous (SC) dose of 75 mg/m² daily for 7 days every 28 days for a median of 9 cycles (range = 1-39).

In the Intent to Treat analysis of 358 patients (179 azacitidine and 179 CCR), azacitidine treatment was associated with a median survival of 24.5 months versus 15 months for those receiving CCR treatment, an improvement of 9.4 months with a stratified log-rank p-value of 0.0001. The hazard ratio describing this treatment effect was 0.58 (95% CI: 0.43, 0.77). The two year survival rates were 50.8% versus 26.2% for patients receiving azacitidine versus CCR (p < 0.0001). The survival benefit was apparent from as early as 3.5 months.



KEY: AZA=azacitidine; CCR=conventional care regimens; CI=confidence interval; HR=hazard ratio

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

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

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

Azacitidine treatment was also associated with a reduction in cytopenias, and their related symptoms. Azacitidine treatment led to a reduced need for red blood cell and platelet transfusions. Of the patients in the azacitidine group who were RBC transfusion dependent at baseline, 45.0% of these patients became RBC transfusion independent during the treatment period, compared with 11.4% of the patients in the combined CCR groups (a statistically significant [p < 0.0001] difference of 33.6% [95% CI: 22.4, 44.6]).

5.2 Pharmacokinetic properties

The effects of renal or hepatic impairment, gender, age, or race on the pharmacokinetics of azacitidine have not been formally studied.

Absorption and distribution

The pharmacokinetics of azacitidine were studied following single 75 mg/m² SC and IV doses. Azacitidine was rapidly absorbed after SC administration with peak plasma azacitidine concentrations of 687 ng/mL (geometric mean) occurring at 0.5 hour (the first sampling point) after dosing. Azacitidine disappeared from plasma rapidly with a mean half-life after SC administration of 41 ± 8 minutes. The absolute bioavailability of SC azacitidine relative to IV azacitidine was approximately 89% based on area under the curve. Following IV dosing, the mean volume of distribution was 76 ± 26 L, systemic clearance was 147 ± 47 L/hr, and C_{max} was 2580 ng/mL. The differences in C_{max} after SC and IV administration are consistent with higher maximum exposure expected following IV versus extravascular drug administration.

Metabolism

Based on *in vitro* data, azacitidine metabolism does not appear to be mediated by cytochrome P450 isoenzymes (CYPs), UDP-glucuronosyltransferases (UGTs), sulfotransferases (SULTs), and glutathione transferases (GSTs).

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.

In vitro studies of azacitidine with cultured human hepatocytes indicate that at concentrations of 1.0 µM to 100 µM, azacitidine does not induce cytochrome P450 1A2, 2C19, or 3A4/5. In studies to assess inhibition of a series of P450 isoenzymes (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4) incubated with azacitidine concentrations of up to 100 µM, azacitidine did not produce inhibition at clinically achievable plasma concentrations. Therefore, CYP enzyme induction or inhibition by azacitidine is unlikely.

Excretion

Urinary excretion is the primary route of elimination of azacitidine and/or its metabolites. Following IV and SC administration of ¹⁴C-azacitidine, 85% and 50% of the dose-administered radioactivity was recovered in urine, respectively, while < 1% was recovered in faeces.

5.3 Preclinical safety data

Azacitidine induces both gene mutations and chromosomal aberrations in bacterial and mammalian cell systems in vitro. The potential carcinogenicity of azacitidine was evaluated in mice and rats. Azacitidine induced tumours of the haematopoietic system in female mice, when administered intraperitoneally 3 times per week for 52 weeks. An increased incidence of tumours in the lymphoreticular system, lung, mammary gland, and skin was seen in mice treated with azacitidine administered intraperitoneally for 50 weeks. A tumorigenicity study in rats revealed an increased incidence of testicular tumours.

Early embryotoxicity studies in mice revealed a 44 % frequency of intrauterine embryonal death (increased resorption) after a single intraperitoneal injection of azacitidine during organogenesis. Developmental abnormalities in the brain have been detected in mice given azacitidine on or before closure of the hard palate. In rats, azacitidine caused no adverse reactions when given pre-implantation, but it was clearly embryotoxic when given during organogenesis. Foetal abnormalities during organogenesis in rats included: CNS anomalies (exencephaly/encephalocele), limb anomalies (micromelia, club foot, syndactyly, oligodactyly) and others (microphthalmia, micrognathia, gastroschisis, oedema, and rib abnormalities).

Administration of azacitidine to male mice 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 resulted in decreased weight of the testes and epididymides, decreased sperm counts, decreased pregnancy rates, an increase in abnormal embryos and increased loss of embryos in mated females (see section 4.4).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol

6.2 Incompatibilities

Azacitidine - Dr Reddy's is incompatible with 5% dextrose solution, volulyte or solutions that contain bicarbonate. These solutions have the potential to increase the rate of degradation of Azacitidine - Dr Reddy's and should therefore be avoided.

6.3 Shelf life

Shelf life is 36 months from date of manufacture stored at or below 25°C, 1 hours reconstituted stored at or below 25°C, 8 hours reconstituted stored at 2° to 8°C (Refrigerate, do not freeze) when reconstituted with unrefrigerated WFI.

Alternatively the shelf life is 22 hours reconstituted stored at 2° to 8°C (Refrigerate, do not freeze) when reconstituted with refrigerated WFI.

6.4 Special precautions for storage

Powder for injection: Store below 25°C.

6.5 Nature and contents of container

Pack sizes: 1 vial

6.6 Special precautions for disposal

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

7 MEDICINE SCHEDULE

Prescription Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

15 February 2018

10 DATE OF REVISION OF THE TEXT

11 January 2022

SUMMARY TABLE OF CHANGES

Section changed	Summary of new information