AUSTRALIAN PRODUCT INFORMATION
VIDAZA® (AZACITIDINE 100 MG) POWDER FOR INJECTION

1 NAME OF THE MEDICINE

Azacitidine

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg azacitidine.

For the full list of excipients, see Section 6.1 [List of excipients].

3 PHARMACEUTICAL FORM

The finished product is supplied in a sterile form for reconstitution as a suspension for subcutaneous injection or reconstitution as a solution with further dilution for intravenous infusion. Vials of Vidaza contain 100 mg of azacitidine and 100 mg mannitol as a white to off-white, sterile lyophilised powder.

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.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Vidaza 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 [CMMoL (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 treatment should only be administered under the supervision of a physician experienced in the use of cancer chemotherapeutic agents. Patients should be premedicated for nausea and vomiting.

4.2.1 Dose

Injectable azacitidine should not be used interchangeably with oral azacitidine due to differences in the exposure, dose and schedule of treatment (see Section 5.2 [Pharmacokinetic Properties]). Healthcare professionals are recommended to verify drug name, dose, and administration route.

First Treatment Cycle

The recommended starting dose for the first treatment cycle, for all patients regardless of baseline haematology laboratory values, is 75 mg/m^2 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 from the previous site and never into areas where the site is tender, bruised, red, or hard.

4.2.2 Dose Modification or Interruption

Dose Adjustment Based on Haematology Laboratory Values

Patients without reduced baseline blood counts (i.e. 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 haematological toxicity is observed following Vidaza treatment (as defined by: Platelets < 50.0 x 10^9/L and/or ANC < 1 x 10^9/L) the next cycle of Vidaza 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 (x 10^9/L)	Platelets (x 10^9/L)	
≤ 1.0	≤ 50.0	50%
> 1.0	> 50.0	100%

*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, ANC < 1.5 x 10^9/L, or platelets < 75.0 x 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 Vidaza therapy should be delayed until the platelet count and the ANC have recovered {counts ≥ 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 ≤ 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 ≥ 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 Section 4.4 [Special Warnings and Precautions for Use]).

4.2.2 Method of Administration

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

If reconstituted Vidaza 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 Vidaza 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.

<u>Instructions for Subcutaneous Administration</u>

Vidaza 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 reconstituted product may be kept in the vial or drawn into a syringe (see Immediate / Delayed Subcutaneous Administration sections below)
- 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
- When more than 1 vial is needed, all of the above steps for preparation of the suspension should be repeated.

The suspension contains azacitidine 25 mg/mL. The maximum recovery of azacitidine is 96% per vial following reconstitution.

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. For doses requiring more than 1 vial, the dose should be equally divided (e.g., dose 150 mg = 6 mL, 2 syringes with 3 mL in each syringe) and injected into two separate sites.

Suspension Stability

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

Reconstituted Vidaza 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.

Immediate Subcutaneous Administration

The reconstituted product may be drawn into a syringe and held at room temperature (25ºC), but must be administered within 1 hour after reconstitution.

Delayed Subcutaneous Administration

The reconstituted product may be kept in the vial or drawn into a syringe. The reconstituted product must be refrigerated immediately.

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

Instructions for Intravenous Administration

Preparation for Intravenous Administration

Reconstitute the appropriate number of Vidaza 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 Vidaza 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

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

Intravenous Administration

Vidaza 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 Vidaza vial.

4.3 CONTRAINDICATIONS

Vidaza is contraindicated in the following:

- patients with known hypersensitivity to azacitidine or to any of the excipients
- patients with advanced malignant hepatic tumours (see Section 4.4 [Special Warnings and Precautions for Use])
- pregnancy
- patients with severe renal impairment (creatinine clearance < 30 mLs/min).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Identified Precautions

Haematological Toxicity

Treatment with Vidaza 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 section 4.2 [Dose and Method of Administration].

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.

Differentiation Syndrome

Cases of differentiation syndrome (also known as retinoic acid syndrome) have been reported in patients receiving injectable azacitidine. Differentiation syndrome may be fatal, and symptoms and clinical findings include respiratory distress, pulmonary infiltrates, fever, rash, pulmonary oedema, peripheral oedema, rapid weight gain, pleural effusions, pericardial effusions, hypotension and renal dysfunction (see Section 4.8 [Adverse effects (undesirable effects)]). Treatment with high-dose IV corticosteroids and haemodynamic monitoring should be considered at first onset of symptoms or signs suggestive of differentiation syndrome. Temporary discontinuation of injectable azacitidine should be considered until resolution of symptoms and if resumed, caution is advised.

Use in Hepatic Impairment

No formal studies have been conducted in patients with hepatic impairment (see Section 5.2 [Pharmacokinetic Properties]). The pivotal safety and efficacy study excluded patients with bilirubin > 1.5 times the upper limit of normal, or with AST or 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 Section 4.3 [Contraindications]).

Use in 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 section 4.2 [Dose and Method of 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 Section 4.2 [Dose and Method of 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 Section 4.3 [Contraindications]).

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

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.

Paediatric Use

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

Effects on 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.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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 are not recommended. Where such medications are considered essential, alternatives that are not strong inducers or inhibitors of metabolising enzymes should be sought.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Azacitidine had adverse effects on male fertility in rodents. Administration of azacitidine to male mice at 9.9 mg/m^2 IP (well below the recommended human daily dose on a mg/m^2 basis) daily for 3 days prior to mating with untreated female mice resulted in decreased fertility and increased pre- and post-implantation loss.

Treatment of male rats three times per week for 6 to 11 weeks at doses well below the recommended human daily dose on a mg/m^2 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 – Pregnancy Category X

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/m^2 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/m^2 (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/m^2 (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 the patient becomes pregnant while taking this drug, the patient should be appraised of the potential hazard to the foetus (see Section 4.3 [Contraindications]). Advise females of reproductive potential to use an effective method of contraception during treatment with azacitidine and for at least 6 months after the last dose.

Use in Male Patients

Men should be advised not to father a child while receiving treatment and for at least 3 months after the last dose. 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).

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.

4.7 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 ADVERSE EFFECTS (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 hypokalaemia.

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 are 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 (≥ 1/10), common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 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, ecchymosispregnan
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 reactions associated with azacitidine treatment were haematological including: thrombocytopenia, neutropenia and leucopenia (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 Section 4.4 [Special Warnings and Precautions for Use]).

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 Section 4.4 [Special Warnings and Precautions for Use]).

Post-Marketing Data

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

- Interstitial lung disease
- Tumour Lysis Syndrome
- Injection Site Necrosis
- Cellulitis
- Necrotizing fasciitis
- Acute febrile neutrophilic dermatosis
- Pyoderma gangrenosum
- Differentiation syndrome
- Cutaneous vasculitis

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

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 Australia, contact the Poisons Information Centre on 13 11 26 for advice on management. 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/m^2, 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

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

Mechanism of Action

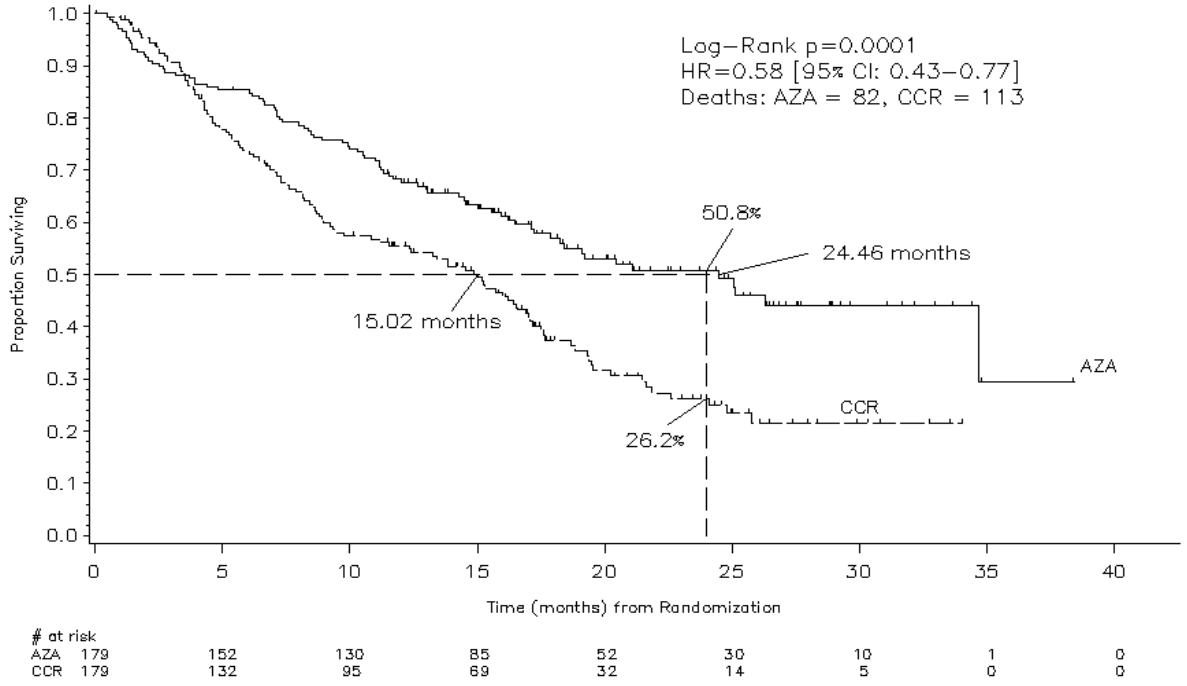
Azacitidine is believed to exert its antineoplastic effects by causing hypomethylation of DNA and direct cytotoxicity on abnormal haematopoietic cells in the bone marrow.

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 Trials

The efficacy and safety of Vidaza 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 mCMMoL 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. Vidaza 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 Vidaza. The primary endpoint of the study was overall survival. Vidaza was administered at a subcutaneous (SC) dose of 75 mg/m^2 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), Vidaza 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 Vidaza 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, poor cytogenetics).

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

Vidaza treatment was also associated with a reduction in cytopenias, and their related symptoms. Vidaza 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/m^2 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, 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

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/m^2 and for 8-36 weeks in rats at doses of 16 60 mg/m^2. These doses are well below the recommended human daily dose (when compared on a mg/m^2 basis). Tumour types included lung, testicular, mammary gland, and skin tumours, lymphomas and tumours of the haematopoietic system.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Each vial contains 100 mg mannitol.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

Unopened Powder Vial

4 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Powder for injection: Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Vidaza is supplied in a colourless single use Type I glass vial sealed with butyl rubber stopper and aluminium seal with plastic button.

Pack sizes: 1 vial

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

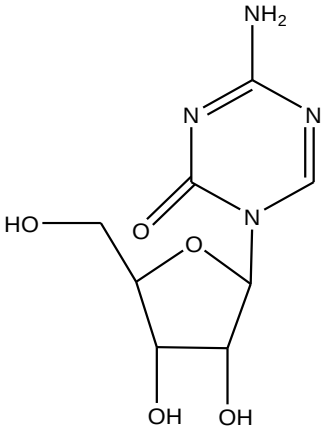
Vidaza is a cytotoxic drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing Vidaza suspensions. Procedures for proper handling and disposal of anticancer drugs should be applied.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical Name

4-amino-1-β-D-ribofuranosyl-s-triazin-2(1*H*)-one

Chemical Structure



CAS Number

320-67-2

Molecular Formula

$C_8H_{12}N_4O_5$

Molecular Weight

244

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8 SPONSOR

Bristol-Myers Squibb Australia Pty Ltd
4 Nexus Court, Mulgrave
Victoria 3170, Australia
Toll free number: 1800 067 567
Email: MedInfo.Australia@bms.com

9 DATE OF FIRST APPROVAL

30 November 2009

10 DATE OF REVISION

22 January 2025

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
8	Update sponsor details

VIDAZA® is a trademark of Celgene Corporation, a Bristol Myers Squibb company.