NAME OF THE MEDICINE

Vidaza (azacitidine 100 mg) Powder for Suspension for Injection

Vidaza contains azacitidine, which is a pyrimidine nucleoside analog of cytidine. Azacitidine is 4-amino-1-β-D-ribofuranosyl-s-triazin-2(1H)-one. The structural formula is as follows:

\[
\begin{align*}
\text{NH}_2 \\
\text{HO} & \quad \text{O} \\
\text{N} & \quad \text{N} \\
\text{O} & \quad \text{N} \\
\text{OH} & \quad \text{OH}
\end{align*}
\]

The empirical formula is \(\text{C}_8\text{H}_{12}\text{N}_4\text{O}_5\).
The molecular weight is 244.
The CAS number is 320-67-2.

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.

The finished product is supplied in a sterile form for reconstitution and subcutaneous injection only. Vials of Vidaza contain 100 mg of azacitidine and 100 mg mannitol as a white to off-white, sterile lyophilised powder.
PHARMACOLOGY

Pharmacotherapeutic group: Antineoplastic agent, 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.

Pharmacokinetics

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 and systemic clearance was 147 ± 47 L/hr.

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 a study to assess inhibition of a series of P450 isoenzymes (1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4) incubated with azacitidine of up to 100 µM, IC₅₀ values could not be determined, therefore, enzyme inhibition by azacitidine at clinically achievable plasma concentrations is unlikely.

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.

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

![Survival Curve](image.png)

Log-Rank p=0.0001
HR=0.58 [95% CI: 0.43–0.77]

Deaths: AZA = 82, CCR = 113

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 and 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 Vidaza 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)).

**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.

**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 Precautions, General)
- pregnancy
- patients with severe renal impairment (creatinine clearance < 30 mLs/min).
PRECAUTIONS

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).

Haematology

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 DOSAGE AND ADMINISTRATION.

Hepatic Impairment

No formal studies have been conducted in patients with hepatic impairment. 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).

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.

Renal Toxicity

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.

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.

**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.

**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.

**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 or 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 PRECAUTIONS, Use in male patients). There have been no animal studies which have examined the effects of azacitidine on female fertility.

**Use in 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/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 the patient becomes pregnant while taking this drug, the patient should be appraised of the potential hazard to the foetus (see CONTRAINDICATIONS).

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.

Interactions with other drugs

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.

Use in children

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.

Use in Patients with Renal Impairment

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)

Use in Patients with Hepatic Impairment

No formal studies have been conducted in patients with hepatic impairment (see PRECAUTIONS, General and Pharmacokinetics). 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.

Laboratory Tests

Liver chemistries and serum creatinine should be obtained prior to initiation of therapy.

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

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.

ADVERSE 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). The following Table 1 shows the treatment-related treatment-emergent 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)

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Number (%) of Patients</th>
<th>Azacitidine (N=175)</th>
<th>BSC Only (N=102)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade 3 or 4</td>
<td>All Grades</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>90 (51.4)</td>
<td>74 (42.3)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>83 (47.4)</td>
<td>76 (43.4)</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>55 (31.4)</td>
<td>10 (5.7)</td>
<td>0</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>22 (12.6)</td>
<td>18 (10.3)</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>71 (40.6)</td>
<td>3 (1.7)</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>48 (27.4)</td>
<td>2 (1.1)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>30 (17.1)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>73 (41.7)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>51 (29.1)</td>
<td>1 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>Injection site pain</td>
<td>31 (17.7)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>25 (14.3)</td>
<td>4 (2.3)</td>
<td>0</td>
</tr>
</tbody>
</table>

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); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data). 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 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 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 using prophylactic antibiotics and/or 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, anti-diarrhoeals 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 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 Precautions).
**Post-marketing Data**
The following events have been reported in the post-marketing setting:
- Interstitial lung disease
- Tumor Lysis Syndrome
- Injection Site Necrosis

**DOSAGE AND ADMINISTRATION**

Vidaza 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.

**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, daily for seven days, followed by a rest period of 21 days (28-day treatment cycle).

Reconstituted Vidaza should be injected subcutaneously.

**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.

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.

**Dosage Adjustment based on Haematology Laboratory Values:**

**Patients without reduced baseline blood counts (i.e. WBC > 3.0 x 10⁹/L and ANC > 1.5 x 10⁹/L, and platelets > 75.0 x 10⁹/L) prior to the first treatment**

If haematological toxicity is observed following Vidaza treatment (as defined by: Platelets < 50.0 x 10⁹/L and/or ANC < 1 x 10⁹/L) 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])). 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.

<table>
<thead>
<tr>
<th>Nadir counts</th>
<th>% Dose in the next cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANC (x 10^9/L)</td>
<td>Platelets (x 10^9/L)</td>
</tr>
<tr>
<td>≤ 1.0</td>
<td>≤ 50.0</td>
</tr>
<tr>
<td>&gt; 1.0</td>
<td>&gt; 50.0</td>
</tr>
</tbody>
</table>

**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:

<table>
<thead>
<tr>
<th>Bone marrow cellularity</th>
<th>% Dose in the next cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recovery ≤ 21 days</td>
<td>Recovery &gt; 21 days</td>
</tr>
<tr>
<td>15-50%</td>
<td>100</td>
</tr>
<tr>
<td>&lt; 15%</td>
<td>100</td>
</tr>
</tbody>
</table>

*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 PRECAUTIONS)

**Preparation of Vidaza:**

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.
Vidaza must be reconstituted with water for injections to form a uniform suspension prior to administration. 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.

**Preparation for Immediate 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 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 Vidaza 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 Vidaza 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.

**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.

Vidaza is administered subcutaneously. 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.

**Stability**

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

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.
OVERDOSAGE

In the event of overdose, the patient should be monitored with appropriate blood counts and should receive supportive treatment, as necessary. There is no known specific antidote for azacitidine overdosage. Contact the Poisons Advisory Centre on 131126 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.

PRESENTATION AND STORAGE CONDITIONS

Each vial contains 100 mg azacitidine and 100 mg mannitol.

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

Storage

Powder for injection: Store below 25°C.

After reconstitution: Reconstituted azacitidine 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.

POISON SCHEDULE OF THE DRUG:

Schedule 4

NAME AND ADDRESS OF THE SPONSOR

Sponsored in Australia by:

Celgene Pty Ltd.
Level 7, 607 St Kilda Road,
Melbourne Victoria - 3004
Australia.

AUST R No: 153080
Sponsored in New Zealand by:

Celgene Limited
Level 7, 28 Brandon Street
Wellington
New Zealand.

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG):
30 November 2009

Date of most recent amendment:
25 October 2011