

Vidaza[®]

azacitidine for injection

1. NAME OF THE MEDICINAL PRODUCT

Vidaza 25 mg/ml powder for suspension for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg azacitidine. After reconstitution, each ml suspension contains 25 mg azacitidine.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for suspension for injection.
White lyophilised powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Vidaza is indicated for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation with:

- intermediate-2 and high-risk myelodysplastic syndromes (MDS) according to the International Prognostic Scoring System (IPSS),
- chronic myelomonocytic leukaemia (CMML) with 10-29% marrow blasts without myeloproliferative disorder,
- acute myeloid leukaemia (AML) with 20-30% blasts and multi-lineage dysplasia, according to World Health Organisation (WHO) classification.

4.2 Posology and method of administration

Vidaza treatment should be initiated and monitored under the supervision of a physician experienced in the use of chemotherapeutic agents. Patients should be premedicated with anti-emetics for nausea and vomiting.

Posology

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, injected subcutaneously, daily for 7 days, followed by a rest period of 21 days (28-day treatment cycle).

It is recommended that patients be treated for a minimum of 6 cycles. Treatment should be continued as long as the patient continues to benefit or until disease progression.

Patients should be monitored for haematologic response/toxicity and renal toxicities (see section 4.4); a delay in starting the next cycle or a dose reduction as described below may be necessary.

Dose adjustment due to haematological toxicity

Haematological toxicity is defined as the lowest count reached in a given cycle (nadir) if platelets fall below 50.0 x 10⁹/l and/or absolute neutrophil count (ANC) below 1 x 10⁹/l.

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

Patients without reduced baseline blood counts (i.e. White Blood Cells (WBC) > 3.0 x 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, 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. However, 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 10⁹/l or ANC < 1.5 x 10⁹/l or platelets < 75.0 x 10⁹/l) prior to the first treatment.

Following Vidaza 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.

If recovery is achieved within 14 days, no dose adjustment is necessary. However, if recovery has not been achieved within 14 days, bone marrow cellularity should be determined. If the bone marrow cellularity is > 50%, no dose adjustments should be made. If bone marrow cellularity is ≤ 50%, treatment should be delayed and the dose reduced according to 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.

Special populations

Renal impairment: No formal studies have been conducted in patients with decreased renal function. Patients with severe organ impairment should be carefully monitored for adverse events. No specific modification to the starting dose is recommended in patients with renal impairment (e.g. baseline serum creatinine or blood urea nitrogen [BUN] ≥ 2 fold above upper limit of normal [ULN] or serum bicarbonate less than 20 mmol/l) prior to starting treatment; subsequent dose modifications should be based on haematology and renal laboratory values. If unexplained reductions in serum bicarbonate levels to less than 20 mmol/l occur, the dose should be reduced by 50% on the next cycle. If unexplained elevations in serum creatinine or BUN to ≥ 2 fold above baseline values and above ULN occur, the next cycle should be delayed until values

return to normal or baseline and the dose should be reduced by 50% on the next treatment cycle (see section 4.4).

Hepatic impairment: No formal studies have been conducted in patients with hepatic impairment (see section 4.4). Patients with severe hepatic organ impairment should be carefully monitored for adverse events. No specific modification to the starting dose is recommended for patients with hepatic impairment prior to starting treatment; subsequent dose modifications should be based on haematology laboratory values. Vidaza is contraindicated in patients with advanced malignant hepatic tumours (see sections 4.3 and 4.4).

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.

Children and adolescents: Vidaza is not recommended for use in children below 18 years due to insufficient data on safety and efficacy.

Laboratory tests

Liver function tests and serum creatinine should be determined prior to initiation of therapy and prior to each treatment cycle. Complete blood counts should be performed prior to initiation of therapy and as needed to monitor response and toxicity, but at a minimum, prior to each treatment cycle.

Method of administration

Reconstituted Vidaza should be injected subcutaneously into the upper arm, thigh or abdomen. Injection sites should be rotated. New injections should be given at least 2.5 cm from the previous site and never into areas where the site is tender, bruised, red, or hardened.

Detailed instructions for the reconstitution and administration procedure for Vidaza are provided in section 6.6.

4.3 Contraindications

Known hypersensitivity to the active substance or to any of the excipients.

Advanced malignant hepatic tumours (see section 4.4).

Lactation (see section 4.6).

4.4 Special warnings and precautions for use

Haematological toxicity

Treatment with azacitidine is associated with anaemia, neutropenia and thrombocytopenia, particularly during the first 2 cycles (see section 4.8). Complete blood counts should be performed as needed to monitor response and toxicity, but at least prior to each treatment cycle. After administration of the recommended dose for the first cycle, the dose for subsequent cycles should be reduced or its administration delayed based on nadir counts and haematological response (see section 4.2). Patients should be advised to promptly report febrile episodes. Patients and physicians are also advised to be observant for signs and symptoms of bleeding.

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 section 4.3).

Renal impairment

Renal abnormalities ranging from elevated serum creatinine to renal failure and death were reported rarely in patients treated with intravenous 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 leukaemia (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 administration delayed (see section 4.2).

Patients with renal impairment should be closely monitored for toxicity since azacitidine and/or its metabolites are primarily excreted by the kidney (see section 4.2).

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 Vidaza in these patients has not been established.

4.5 Interaction with other medicinal products and other forms of interaction

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); interactions related to these metabolizing enzymes *in vivo* are therefore considered unlikely.

Clinically significant inhibitory or inductive effects of azacitidine on cytochrome P450 enzymes are unlikely (see section 5.2).

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

4.6 Pregnancy and lactation

Pregnancy

There are no adequate data on the use of azacitidine in pregnant women. Studies in mice have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Based on results from animal studies and its mechanism of action, azacitidine should not be used during pregnancy, especially during the first trimester, unless clearly necessary. The advantages of treatment should be weighed against the possible risk for the foetus in every individual case.

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

Lactation

It is not known whether azacitidine or its metabolites are excreted in human milk. Due to the potential serious adverse reactions in the nursing child, breast-feeding is contraindicated during azacitidine therapy.

Fertility

There are no human data on the effect of azacitidine on fertility. In animals, adverse effects of azacitidine on male fertility have been documented (see section 5.3). Men should be advised not to father a child while receiving treatment and must use effective contraception during and up to 3 months after treatment. Before starting treatment, male patients should be advised to seek counselling on sperm storage.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

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

The most commonly reported adverse reactions with azacitidine treatment were haematological reactions (71.4%) including thrombocytopenia, neutropenia and leukopenia (usually Grade 3-4), gastrointestinal events (60.6%) including nausea, vomiting (usually Grade 1-2) or injection site reactions (77.1%; usually Grade 1-2).

The most common serious adverse reactions (> 2%) noted from the pivotal study (AZA PH GL 2003 CL 001) and also reported in the supporting studies (CALGB 9221 and CALGB 8921) included febrile neutropenia (8.0%) and anaemia (2.3%). Other less frequently reported serious adverse reactions (< 2%) included neutropenic sepsis, pneumonia, thrombocytopenia and haemorrhagic events (e.g. cerebral haemorrhage).

The following table contains the adverse reactions for which a causal relationship with azacitidine treatment could reasonably be established. 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 ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ 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.

System Organ Class	Very common	Common	Uncommon
Infections and infestations	pneumonia, nasopharyngitis	neutropenic sepsis, upper respiratory tract infection, urinary tract infection, sinusitis, pharyngitis, rhinitis, herpes simplex	
Blood and lymphatic system disorders	febrile neutropenia, neutropenia, leukopenia, thrombocytopenia, anaemia	bone marrow failure, pancytopenia	
Immune system disorders			hypersensitivity reactions
Metabolism and nutrition disorders	anorexia	hypokalemia	
Psychiatric disorders		confusional state, anxiety, insomnia	
Nervous system disorders	dizziness, headache	intracranial haemorrhage, lethargy	
Eye disorders		eye haemorrhage, conjunctival haemorrhage	
Vascular disorders		hypertension, hypotension, haematoma	
Respiratory, thoracic and mediastinal disorders	dyspnoea	dyspnoea exertional, pharyngolaryngeal pain	
Gastrointestinal disorders	diarrhoea, vomiting, constipation, nausea, abdominal pain	gastrointestinal haemorrhage, haemorrhoidal haemorrhage, stomatitis, gingival bleeding, dyspepsia	
Skin and subcutaneous tissue disorders	petechiae, pruritus, rash, ecchymosis	purpura, alopecia, erythema, rash macular	
Musculoskeletal, and connective tissue disorders	arthralgia	myalgia, musculoskeletal pain	
Renal and urinary disorders		haematuria	
General disorders and administration site conditions	fatigue, pyrexia, chest pain, injection site erythema, injection site pain, injection site reaction (unspecified)	injection site: bruising, haematoma, induration, rash, pruritus, inflammation, discoloration, nodule and haemorrhage, malaise	
Investigations		weight decreased	

Haematologic adverse reactions

The most commonly reported adverse reactions associated with azacitidine treatment were haematological including thrombocytopenia, neutropenia and leukopenia, and were usually Grade 3 or 4. 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, prophylactic antibiotics and/or growth factor support (e.g. G-CSF) for neutropenia and transfusions for anaemia or thrombocytopenia as required.

Infections

Myelosuppression may lead to neutropenia and an increased risk of infection. Serious adverse reactions such as neutropenic sepsis (0.8%) and pneumonia (2.5%) were reported in patients receiving azacitidine. Infections may be managed with the use of anti-infectives plus growth factor support (e.g. G-CSF) for neutropenia.

Bleeding

Bleeding may occur with patients receiving azacitidine. Serious adverse reactions such as gastrointestinal haemorrhage (0.8%) and intracranial haemorrhage (0.5%) have been reported. Patients should be monitored for signs and symptoms of bleeding, particularly those with pre-existing or treatment-related thrombocytopenia.

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, rash, 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.

4.9 Overdose

One case of overdose with azacitidine was reported during clinical trials. A patient experienced diarrhoea, nausea, and vomiting after receiving a single intravenous dose of approximately 290 mg/m², almost 4 times the recommended starting dose.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agent, Pyrimidine analogues;
ATC code: L01BC07.

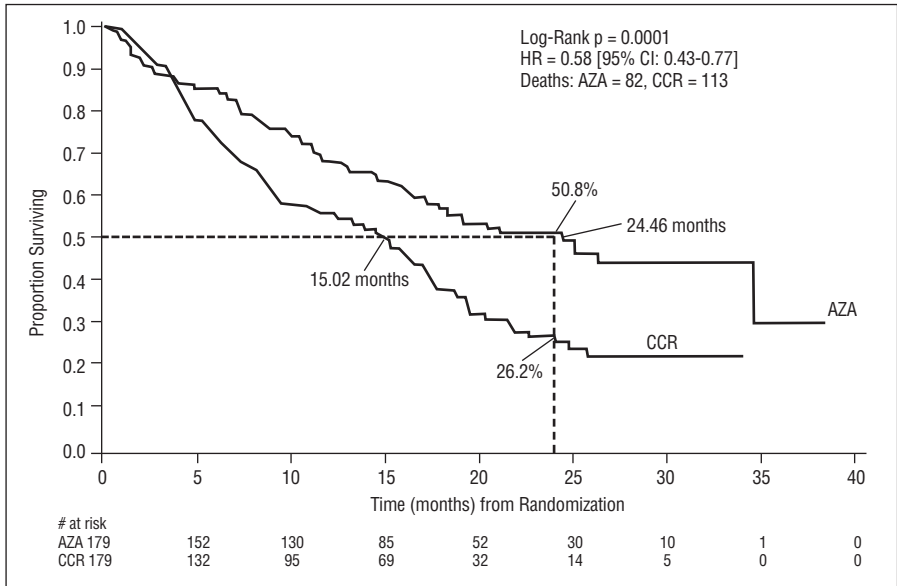
Mechanism of action

Azacitidine is believed to exert its antineoplastic effects by multiple mechanisms including cytotoxicity on abnormal haematopoietic cells in the bone marrow and hypomethylation of DNA. The cytotoxic effects of azacitidine may result from multiple mechanisms, including inhibition of DNA, RNA and protein synthesis, incorporation into RNA and DNA, and activation of DNA damage pathways. Non-proliferating cells are relatively insensitive to azacitidine. Incorporation of azacitidine into DNA results in the inactivation of DNA methyltransferases, leading to hypomethylation of DNA. DNA hypomethylation of aberrantly methylated genes involved in normal cell cycle regulation, differentiation and death pathways may result in gene re-expression and restoration of cancer-suppressing functions to cancer cells. The relative importance of DNA hypomethylation versus cytotoxicity or other activities of azacitidine to clinical outcomes has not been established.

Clinical efficacy and safety

The efficacy and safety of Vidaza were studied in an international, multicenter, controlled, open-label, randomised, parallel-group, Phase 3 comparative study (AZA PH GL 2003 CL 001) in patients with: intermediate-2 and high-risk MDS according to the International Prognostic Scoring System (IPSS), refractory anaemia with excess blasts (RAEB), refractory anaemia with excess blasts in transformation (RAEB-T) and modified chronic myelomonocytic leukaemia (mCMML) according to the French American British (FAB) classification system. RAEB-T patients (21-30% blasts) are now considered to be AML patients under the current WHO classification system. Azacitidine plus best supportive care (BSC) (n = 179) was compared to conventional care regimens (CCR). CCR consisted of BSC alone (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 randomisation. Patients received this pre-selected regimen if not randomised to Vidaza. As part of the inclusion criteria, patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. Patients with secondary MDS were excluded from the study. The primary endpoint of the study was overall survival. Vidaza was administered at a subcutaneous dose of 75 mg/m² daily for 7 days, followed by a rest period of 21 days (28 day treatment cycle) for a median of 9 cycles (range = 1-39) and a mean of 10.2 cycles. Within the Intent to Treat population (ITT), the median age was 69 years (range 38 to 88 years).

In the ITT analysis of 358 patients (179 azacitidine and 179 CCR), Vidaza treatment was associated with a median survival of 24.46 months versus 15.02 months for those receiving CCR treatment, a difference of 9.4 months, with a stratified log-rank p-value of 0.0001. The hazard ratio for the treatment effect was 0.58 (95% CI: 0.43, 0.77). The two-year survival rates were 50.8% in patients receiving azacitidine versus 26.2% in patients receiving CCR (p < 0.0001).



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 induction chemotherapy plus BSC) utilised 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, including monosomy 7).

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

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 (RBC) 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)). In patients who were RBC transfusion dependent at baseline and became independent, the median duration of RBC transfusion independence was 13 months in the azacitidine group.

Response was assessed by the investigator or by the Independent Review Committee (IRC). Overall response (complete remission [CR] + partial remission [PR]) as determined by the investigator was 29% in the azacitidine group and 12% in the combined CCR group ($p = 0.0001$). Overall response (CR + PR) as determined by the IRC in AZA PH GL 2003 CL 001 was 7% (12/179) in the azacitidine group compared with 1% (2/179) in the combined CCR group ($p = 0.0113$). The differences between the IRC and investigator assessments of response were a consequence of the International Working Group (IWG) criteria requiring improvement in peripheral blood counts and maintenance of these improvements for a minimum of 56 days. A survival benefit was also demonstrated in patients that had not achieved a complete/partial response following azacitidine treatment. Haematological improvement (major or minor) as determined by the IRC was achieved in 49% of patients receiving azacitidine compared with 29% of patients treated with combined CCR ($p < 0.0001$).

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

5.2 Pharmacokinetic properties

The pharmacokinetics of azacitidine were studied following single 75 mg/m² doses given by subcutaneous and intravenous administration.

Absorption

Azacitidine was rapidly absorbed after subcutaneous administration with peak plasma azacitidine concentrations of 750 ± 403 ng/ml occurring at 0.5 h (the first sampling point) after dosing. The absolute bioavailability of azacitidine after subcutaneous relative to intravenous administration was approximately 89% based on area under the curve (AUC).

Distribution

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

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 $1.0 \mu\text{M}$ to $100 \mu\text{M}$ (i.e. up to approximately 30 fold higher than clinically achievable concentrations), azacitidine does not induce cytochrome P450 isoenzymes (CYP) 1A2, 2C19, or 3A4 or 3A5. In a study to assess inhibition of a series of P450 isoenzymes (CYP 1A2, 2C9, 2C19, 2D6, 2E1 and 3A4) incubated with $100 \mu\text{M}$ azacitidine, IC_{50} values could not be determined, therefore, enzyme inhibition by azacitidine at clinically achievable plasma concentrations is unlikely. The potential to inhibit CYP2B6 or 2C8 has not been studied.

Excretion

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

Special populations

The effects of renal or hepatic impairment (see section 4.2), gender, age, or race on the pharmacokinetics of azacitidine have not been formally studied.

Pharmacogenomics

The effect of known cytidine deaminase polymorphisms on azacitidine metabolism has not been formally investigated.

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 effects when given pre-implantation, but it was clearly embryotoxic during when given during organogenesis. Foetal abnormalities caused during organogenesis included: CNS anomalies (exencephaly/encephalocele), limb anomalies (micromelia, club foot, syndactyly, oligodactyly) and others (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 (E421)

6.2 Incompatibilities

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

6.3 Shelf life

Unopened powder vial:

4 years

After reconstitution:

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

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

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage conditions of the reconstituted medicinal product, see section 6.3.

6.5 Nature and contents of container

Colourless type I 30 ml glass vial sealed with butyl elastomeric stopper and aluminium seal with polypropylene plastic button.

Pack size: 1 vial of 100 mg azacitidine.

6.6 Special precautions for disposal and other handling

Recommendations for safe handling

Vidaza is a cytotoxic medicinal product and, as with other potentially toxic compounds, caution should be exercised when handling and preparing azacitidine suspensions.

Procedures for proper handling and disposal of anticancer medicinal products should be applied.

If reconstituted azacitidine comes into contact with the skin, immediately and thoroughly wash with soap and water. If it comes into contact with mucous membranes, flush thoroughly with water.

Reconstitution procedure

1. The following supplies should be assembled:
 - Vial(s) of azacitidine; vial(s) of water for injections; nonsterile surgical gloves;
 - Alcohol wipes; 5 ml injection syringe(s) with needle(s).
2. 4 ml of water for injections should be drawn into the syringe, making sure to purge any air trapped within the syringe.
3. The needle of the syringe containing the 4 ml of water for injections should be inserted through the rubber top of the azacitidine vial followed by injection of the water for injections into the vial.

4. Following removal of the syringe and needle, the vial should be vigorously shaken until a uniform cloudy suspension is achieved. After reconstitution each ml of suspension will contain 25 mg of azacitidine (100 mg/4 ml). The reconstituted product is a homogeneous, cloudy suspension, free of agglomerates. The product should be discarded if it contains large particles or agglomerates.
5. The rubber top should be cleaned and a new syringe with needle inserted. The vial should then be turned upside down, making sure the needle tip is below the level of the liquid. The plunger should then be pulled back to withdraw the amount of medicinal product required for the proper dose, making sure to purge any air trapped within the syringe. The syringe with needle should then be removed from the vial and the needle disposed of.
6. A fresh subcutaneous needle (recommended 25 gauge) should then be firmly attached to the syringe. The needle should not be purged prior to injection, in order to reduce the incidence of local injection site reactions.
7. If needed (doses over 100 mg) all the above steps for preparation of the suspension should be repeated. For doses greater than 100 mg (4 ml), the dose should be equally divided into 2 syringes (e.g. dose 150 mg = 6 ml, 2 syringes with 3 ml in each syringe).
8. The contents of the dosing syringe must be re-suspended immediately prior to administration. The temperature of the suspension at the time of injection should be approximately 20°C-25°C. To re-suspend, vigorously roll the syringe between the palms until a uniform, cloudy suspension is achieved. The product should be discarded if it contains large particles or agglomerates.

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

Calculation of an individual dose

The total dose, according to the body surface area (BSA) can be calculated as follows:

$$\text{Total dose (mg)} = \text{Dose (mg/m}^2\text{)} \times \text{BSA (m}^2\text{)}$$

The following table is provided only as an example of how to calculate individual azacitidine doses based on an average BSA value of 1.8 m².

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

Method of administration

Reconstituted Vidaza should be injected subcutaneously (insert the needle at a 45-90° angle) using a 25-gauge needle into the upper arm, thigh or abdomen.

Doses greater than 4 ml should be injected into two separate sites.

Injection sites should be rotated. New injections should be given at least 2.5 cm from the previous site and never into areas where the site is tender, bruised, red, or hardened.

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

7. MARKETING AUTHORISATION HOLDER

Celgene Europe Ltd
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Windsor
SL4 1NA
United Kingdom
Tel: +44 1753 240600
Fax: +44 1753 240656

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/488/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/12/2008

10. DATE OF REVISION OF THE TEXT

20/10/2009

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azacitidine for injection

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