1. NAME OF THE MEDICINAL PRODUCT

Vidaza® Powder For Suspension For Injection 100mg/vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 100 mg azacitidine. After reconstitution, each mL of 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/m^2 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 for 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.

Vidaza® should not be used interchangeably with oral azacitidine. Due to differences in the exposure, the dose and schedule recommendations for oral azacitidine are different from those for injectable azacitidine. Healthcare professionals are recommended to verify the name of the medicinal product, dose and administration route.

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 prior to initiation of therapy and as needed to monitor response and toxicity, but at a minimum, prior to each treatment cycle.

Dose adjustment due to haematological toxicity
Haematological toxicity is defined as the lowest count reached (nadir) in a given cycle if platelets ≤ 50.0 x 10^9/L and/or absolute neutrophil count (ANC) ≤ 1 x 10^9/L.

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

Patients without reduced baseline blood counts (i.e. White Blood Cells (WBC) ≥ 3.0 x 10^9/L and ANC ≥ 1.5 x 10^9/L, and platelets ≥ 75.0 x 10^9/L) prior to the first treatment
If haematological toxicity is observed following Vidaza® treatment, the next cycle of the 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.

Cycle Nadir count		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 or ANC < 1.5 x 10^9/L or platelets < 75.0 x 10^9/L) prior to the first treatment
Following Vidaza® treatment, if the decrease in WBC or ANC or platelets from that prior to treatment is ≤ 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 next cycle duration should return to 28 days.

Special populations
Elderly patients
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.

Patients with renal impairment
Azacitidine can be administered to patients with renal impairment without initial dose adjustment (see section 5.2). 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 blood urea nitrogen (BUN) to ≥ 2-fold above baseline values and above upper limit of normal (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).

Patients with 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).

Paediatric population
The safety and efficacy of Vidaza® in children aged 0-17 years have not yet been established. No data are available.

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.

After reconstitution, the suspension should not be filtered. For instructions on reconstitution of the medicinal product before administration, see section 6.5.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Advanced malignant hepatic tumours (see section 4.4).

Breast-feeding (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 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 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 should be advised to report oliguria and anuria to the health care provider immediately.

Although no clinically relevant differences in the frequency of adverse reactions were noted between subjects with normal renal function compared to those with renal impairment, 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).

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 prior to initiation of therapy and as needed to monitor response and toxicity, but at a minimum, prior to each treatment cycle, see also section 4.8.

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 registration study (AZA PH GL 2003 CL 001) and therefore the safety and efficacy of azacitidine in these patients has not been established. Recent data from a clinical study in patients with a known history of cardiovascular or pulmonary disease showed a significantly increased incidence of cardiac events with azacitidine (see section 4.8). It is therefore advised to exercise caution when prescribing azacitidine to these patients. Cardiopulmonary assessment before and during the treatment should be considered.

Necrotising fasciitis
Necrotising fasciitis, including fatal cases, have been reported in patients treated with Vidaza®. Vidaza® therapy should be discontinued in patients who develop necrotising fasciitis and appropriate treatment should be promptly initiated.

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). 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.

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 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females
Women of childbearing potential have to use effective contraception during and for at least 6 months after treatment. Men should be advised not to father a child while receiving treatment and must use effective contraception during and for at least 3 months after treatment.

Pregnancy
There are no adequate data from 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.

Breast-feeding
It is unknown whether azacitidine/ 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 reactions with azacitidine use on male fertility have been documented (see section 5.3). Before starting treatment, male patients should be advised to seek counselling on sperm storage.

4.7 Effects on ability to drive and use machines

Azacitidine has minor or moderate influence on the ability to drive and use machines. Fatigue has been reported with the use of azacitidine. Therefore, caution is recommended when driving or operating machines.

4.8 Undesirable effects

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

The most common serious adverse reactions noted from the pivotal study (AZA PH GL 2003 CL 001) included febrile neutropenia (8.0%) and anaemia (2.3%), which were also reported in the supporting studies (CALGB 9221 and CALGB 8921). Other serious adverse reactions from these 3 studies included infections such as neutropenic sepsis (0.8%) and pneumonia (2.5%) (some with fatal outcome), thrombocytopenia (3.5%), hypersensitivity reactions (0.25%) and haemorrhagic events (e.g. cerebral haemorrhage [0.5%], gastrointestinal haemorrhage [0.8%] and intracranial haemorrhage [0.5%]).

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).

Tabulated list of adverse reactions
Table 1 below contains adverse reactions associated with azacitidine treatment obtained from the main clinical studies in MDS and AML and post marketing surveillance.

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 reactions are presented in the table below according to the highest frequency observed in any of the main clinical studies.

Table 1: Adverse reactions reported in patients with MDS or AML treated with azacitidine (clinical studies and post-marketing)

System Organ Class	Very common	Common	Uncommon	Rare	Not Known
Infections and infestations	pneumonia* (including bacterial, viral and fungal), nasopharyngitis	sepsis* (including bacterial, viral and fungal), neutropenic sepsis*, respiratory tract infection (includes upper and bronchitis), urinary tract infection, cellulitis, diverticulitis, oral fungal infection, sinusitis, pharyngitis, rhinitis, herpes simplex, skin infection			necrotising fasciitis*
Neoplasms benign, malignant and unspecified (including cysts and polyps)					differentiation syndrome*,[a]
Blood and lymphatic system disorders	febrile neutropenia*, neutropenia, leukopenia, thrombocytopenia, anaemia	Pancytopenia*, bone marrow failure			
Immune system disorders			hypersensitivity reactions		
Metabolism and nutrition disorders	anorexia, decreased appetite, hypokalemia	dehydration		tumour lysis syndrome	

System Organ Class	Very common	Common	Uncommon	Rare	Not Known
Psychiatric disorders	insomnia	confusional state, anxiety			
Nervous system disorders	dizziness, headache	intracranial haemorrhage*, syncope, somnolence, lethargy			
Eye disorders		eye haemorrhage, conjunctival haemorrhage			
Cardiac disorders		pericardial effusion	pericarditis		
Vascular disorders		hypotension*, hypertension, orthostatic hypotension, haematoma			
Respiratory, thoracic and mediastinal disorders	dyspnoea, epistaxis	pleural effusion, dyspnoea exertional, pharyngolaryngeal pain		Interstitial lung disease	
Gastrointestinal disorders	diarrhoea, vomiting, constipation, nausea, abdominal pain (includes upper and abdominal discomfort)	gastrointestinal haemorrhage* (includes mouth haemorrhage), haemorrhoidal haemorrhage, stomatitis, gingival bleeding, dyspepsia			
Hepatobiliary disorders			hepatic failure*, progressive hepatic coma		
Skin and subcutaneous tissue disorders	petechiae, pruritus (includes generalized), rash, ecchymosis	purpura, alopecia, urticaria, erythema, rash macular	acute febrile neutrophilic dermatosis, pyoderma gangrenosum		cutaneous vasculitis
Musculoskeletal, and connective tissue disorders	arthralgia, musculoskeletal pain (includes back, bone and pain in extremity)	muscle spasms, myalgia			
Renal and urinary disorders		renal failure*, haematuria, elevated serum creatinine	renal tubular acidosis		

System Organ Class	Very common	Common	Uncommon	Rare	Not Known
General disorders and administration site conditions	pyrexia*, fatigue, asthenia, chest pain, injection site erythema, injection site pain, injection site reaction (unspecified)	bruising, haematoma, induration, rash, pruritus, inflammation, discoloration, nodule and haemorrhage (at injection site), Malaise, chills, catheter site hemorrhage		injection site necrosis (at injection site)	
Investigations	weight decreased				

* = rarely fatal cases have been reported

[a] = see section 4.4

Description of selected adverse reactions

Haematologic adverse reactions

The most commonly reported (≥ 10%) haematological adverse reactions associated with azacitidine treatment include anaemia, thrombocytopenia, neutropenia, febrile 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 sepsis, including neutropenic sepsis and pneumonia were reported in patients receiving azacitidine, some with a fatal outcome. 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 and intracranial haemorrhage 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 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 discontinuation of azacitidine, or reduction of azacitidine dose in the pivotal study. The majority of adverse reactions occurred during the first 2 cycles of treatment 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 medicinal products (NSAIDs). These cutaneous reactions have to be distinguished from soft tissue infections, sometimes occurring at injection site. Soft tissue infections, including cellulitis and

necrotising fasciitis in rare cases leading to death, have been reported with azacitidine in the post marketing setting. For clinical management of infectious adverse reactions, see section 4.8 Infections.

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 and haematuria to renal tubular acidosis, renal failure and death were reported in patients treated with azacitidine (see section 4.4).

Hepatic adverse reactions
Patients with extensive tumour burden due to metastatic disease have been reported to experience hepatic failure, progressive hepatic coma and death during azacitidine treatment (see section 4.4).

Cardiac events
Data from a clinical study allowing enrolment of patients with known history of cardiovascular or pulmonary disease showed an increase in cardiac events in patients with newly diagnosed AML treated with azacitidine (see section 4.4).

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

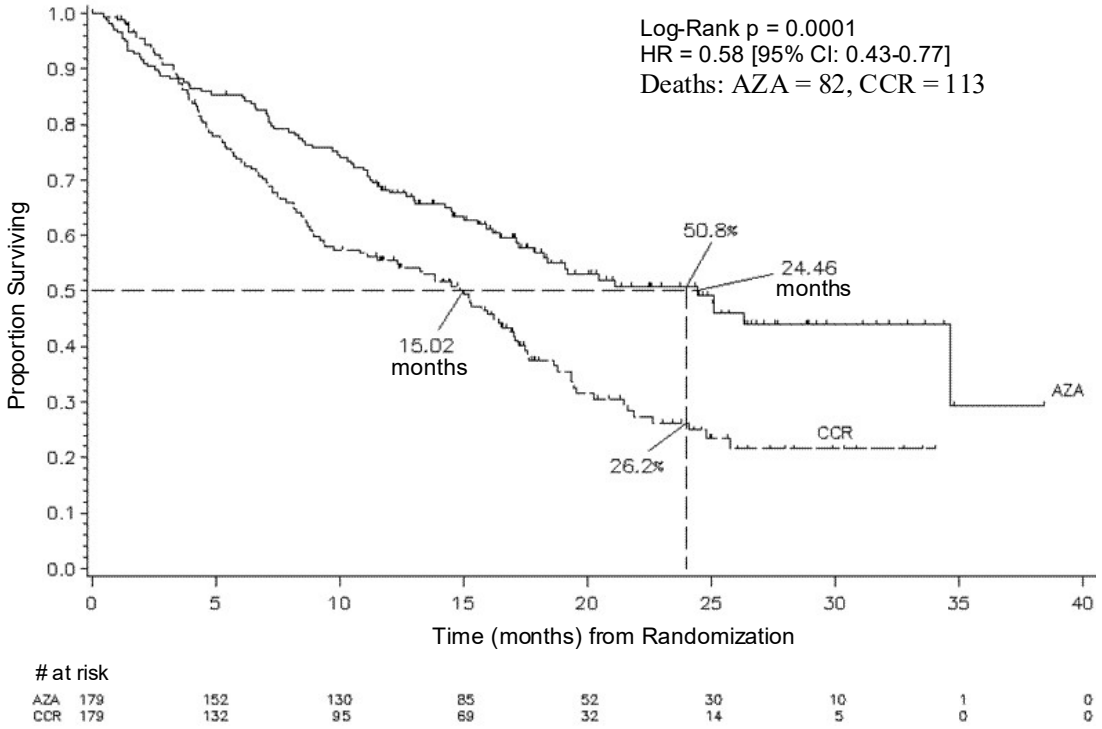
Pharmacotherapeutic group: Antineoplastic agents, Pyrimidine analogues; ATC code: L01BC07

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, multicentre, controlled, open-label, randomised, parallel-group, Phase 3 comparative study (AZA PH GL 2003 CL 001) in adult 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/m^2 daily for 7 days, followed by a rest period of 21 days (28-day treatment cycle) for a median of 9 cycles (range = 1-39) 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 (HR) 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

Absorption
Following subcutaneous administration of a single 75 mg/m^2 dose, azacitidine was rapidly absorbed with peak plasma concentrations of 750 ± 403 ng/mL occurring at 0.5 h after dosing (the first sampling point). The absolute bioavailability of azacitidine after subcutaneous relative to intravenous administration (single 75 mg/m^2 doses) was approximately 89 % based on area the under the curve (AUC).

Area under the curve and maximum plasma concentration (C_{max}) of subcutaneous admiminstration of azacitidine were approximately proportional within the 25 to 100 mg/m^2 dose range.

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

Biotransformation
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).

Azacitidine undergoes spontaneous hydrolysis and deamination mediated by cytidine deaminase. In human liver S9 fractions, formation of metabolites was independent of NADPH implying that azacitidine metabolism was not mediated by cytochrome P450 isoenzymes. An *in vitro* study of azacitidine with cultured human hepatocytes indicates that at concentrations of 1.0 µM to 100 µM (i.e. up to approximately 30-fold higher than clinically achievable concentrations), azacitidine does not induce CYP 1A2, 2C19, or 3A4 or 3A5. In studies to assess inhibition of a series of P450 isoenzymes (CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4) azacitidine up to 100 µM did not produce inhibition. Therefore, CYP enzyme induction or inhibition by azacitidine at clinically achievable plasma concentrations is unlikely.

Elimination
Azacitidine is cleared rapidly from plasma with a mean elimination half-life ($t_{½}$) after subcutaneous administration of 41 ± 8 minutes. No accumulation occurs after subcutaneous administration of 75 mg/m^2 azacitidine once daily for 7 days. Urinary excretion is the primary route of elimination of azacitidine and/or its metabolites. Following intravenous and subcutaneous administration of ^{14}C-azacitidine, 85 and 50% of the administered radioactivity was recovered in urine respectively, while < 1% was recovered in faeces.

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

Renal impairment
Renal impairment has no major effect on the pharmacokinetic exposure of azacitidine after single and multiple subcutaneous administrations. Following subcutaneous administration of a single 75 mg/m^2 dose, mean exposure values (AUC and C_{max}) from subjects with mild, moderate and severe renal impairment were increased by 11-21%, 15-27%, and 41-66%, respectively, compared to normal renal function subjects. However, exposure was within the same general range of exposures observed for subjects with normal renal function. Azacitidine can be administered to patients with renal impairment without initial dose adjustment provided these patients are monitored for toxicity since azacitidine and/or its metabolites are primarily excreted by the kidney.

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 reactions when given pre-implantation, but it was clearly embryotoxic when given during organogenesis. Foetal abnormalities during organogenesis in rats included: CNS anomalies (exencephaly/encephalocele), limb anomalies (micromelia, club foot, syndactyly, oligodactyly) and others (microphthalmia, micrognathia, gastroschisis, oedema, and rib abnormalities).

Administration of azacitidine to male mice prior to mating with untreated female mice resulted in decreased fertility and loss of offspring during subsequent embryonic and postnatal development. Treatment of male rats resulted in decreased weight of the testes and epididymides, decreased sperm counts, decreased pregnancy rates, an increase in abnormal embryos and increased loss of embryos in mated females (see section 4.6).

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 6.3 and 6.5.

6.3 Special precautions for storage

Store the medicinal product in its original package at below 30^0 C.

After reconstitution:
When Vidaza® is reconstituted using water for injections that has not been refrigerated, 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.

The shelf life of the reconstituted medicinal product can be extended by reconstituting with refrigerated (2°C to 8°C) water for injections. When Vidaza® is reconstituted using refrigerated (2°C to 8°C) water for injections, the chemical and physical in-use stability of the reconstituted medicinal product has been demonstrated at 2°C to 8°C for 22 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 when reconstituted using water for injections that has not been refrigerated or not longer than 22 hours when reconstituted using refrigerated (2°C to 8°C) water for injections.

6.4 Nature and contents of container

Colourless type I glass vial sealed with butyl elastomeric stopper and aluminium seal with polypropylene plastic button, containing 100 mg of azacitidine.

Pack size: 1 vial

6.5 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
Vidaza® should be reconstituted with water for injections. The shelf life of the reconstituted medicinal product can be extended by reconstituting with refrigerated (2°C to 8°C) water for injections. Details on storage of the reconstituted product are provided below.

1. The following supplies should be assembled:
   Vial(s) of azacitidine; vial(s) of water for injections; non-sterile 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. Do not filter the suspension after reconstitution since this could remove the active substance. It must be taken into account that filters are present in some adaptors, spikes and closed systems; therefore such systems should not be used for administration of the drug after reconstitution.

5. The rubber top should be cleaned and a new syringe with needle inserted into the vial. 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. When more than 1 vial is needed all the above steps for preparation of the suspension should be repeated. 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. Due to retention in the vial and needle, it may not be feasible to withdraw all of the suspension from the vial.
8. The contents of the dosing syringe must be re-suspended immediately prior to administration. The syringe filled with reconstituted suspension should be allowed up to 30 minutes prior to administration to reach a temperature of approximately 20ºC-25ºC. If the elapsed time is longer than 30 minutes, the suspension should be discarded appropriately and a new dose prepared. 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.

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

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

Total dose (mg) = Dose (mg/m^2) x BSA (m^2)

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 m^2.

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 45-90º 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 medicinal product or waste material should be disposed of in accordance with local requirements.

Product Registration Holder:
DKSH Malaysia Sdn Bhd, B-11-01 The Ascent Paradigm, No. 1 Jalan SS7/26A Kelana Jaya, 47301 Petaling Jaya, Selangor, Malaysia

Date of revision of PI : 14 February 2024
20240214/VID PI/MY