ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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 of suspension contains 25 mg azacitidine.

For the 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 (HSCT) 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.

Vidaza is indicated for the treatment of adult patients aged 65 years or older who are not eligible for HSCT with AML with >30% marrow blasts according to the 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 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.

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 in a given cycle (nadir) 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 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.

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

*Recovery = counts ≥ nadir count + (0.5 x [baseline count – nadir count])

Patients with reduced baseline blood counts (i.e. WBC < 3.0 x 10^9/l 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 cycle duration should return to 28 days.

<u>Special populations</u>
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 6.6.

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 studies (AZA PH GL 2003 CL 001 and AZA-AML-001) and therefore the safety and efficacy of azacitidine in these patients has not been established. Recent data from a clinical trial 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.

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 and men must use effective contraception during and up to 3 months after treatment.

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.

Breast-feeding
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 reactions with azacitidine use 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

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
Adult population with MDS, CMML and AML (20-30% marrow blasts)
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).

Adult population aged 65 years or older with AML with > 30% marrow blasts
The most common serious adverse reactions (≥ 10%) noted from AZA-AML-001 within the azacitidine treatment arm included febrile neutropenia (25.0%), pneumonia (20.3%), and pyrexia (10.6%). Other less frequently reported serious adverse reactions in the azacitidine treatment arm included sepsis (5.1%), anaemia (4.2%), neutropenic sepsis (3.0%), urinary tract infection (3.0%), thrombocytopenia (2.5%), neutropenia (2.1%), cellulitis (2.1%), dizziness (2.1%) and dyspnoea (2.1%).

The most commonly reported (≥ 30%) adverse reactions with azacitidine treatment were gastrointestinal events, including constipation (41.9%), nausea (39.8%), and diarrhoea (36.9%), (usually Grade 1-2), general disorders and administration site conditions including pyrexia (37.7%; usually Grade 1-2) and haematological events, including febrile neutropenia (32.2%) and neutropenia (30.1%), (usually Grade 3-4).

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: ADRs 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 *
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	
Psychiatric disorders	insomnia	confusional state, anxiety			
Nervous system disorders	dizziness, headache	intracranial haemorrhage*, syncope, somnolence, lethargy			

System Organ Class	Very common	Common	Uncommon	Rare	Not Known
Eye disorders		eye haemorrhage, conjunctival haemorrhage			
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		
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		
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

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 studies. 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 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 trial allowing enrolment of patients with known history of cardiovascular or pulmonary disease showed a statistically significant increase in cardiac events in patients with newly diagnosed AML treated with azacitidine (see section 4.4).

Elderly population
There is limited safety information available with azacitidine in patients ≥85 years (with 14 [5.9%] patients ≥85 years in AZA-AML-001 study).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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/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

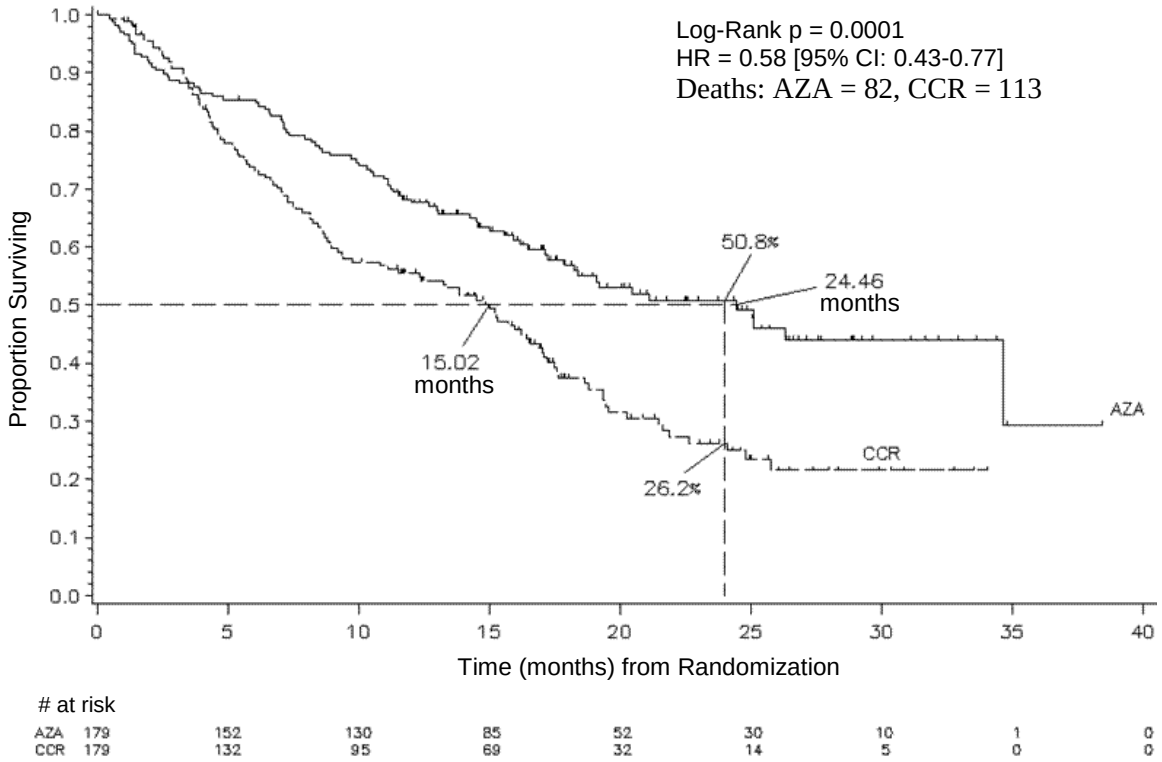
Mechanism of action
Azacitidine is believed to exert its antineoplastic effects by multiple mechanisms including cytotoxicity on abnormal haematopoietic cells in the bone marrow and hypomethylation of DNA. The cytotoxic effects of azacitidine may result from multiple mechanisms, including inhibition 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

Adult population (MDS, CMML and AML [20-30% marrow blasts])
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 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 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 %).

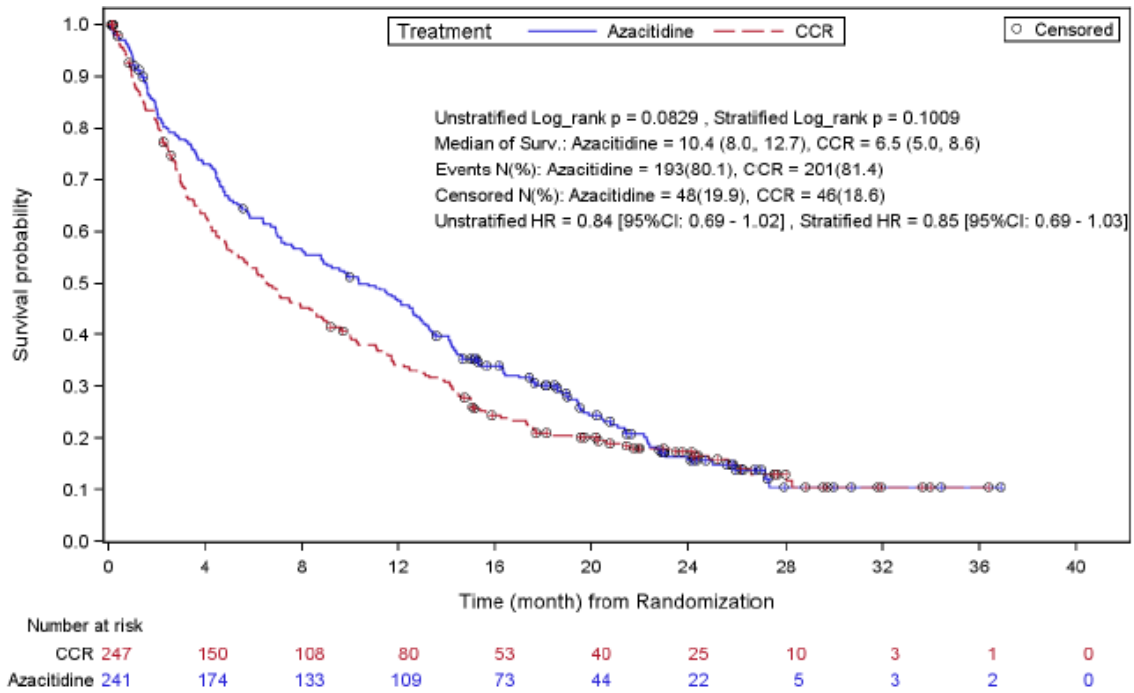
Adult population aged 65 years or older with AML with > 30% marrow blasts
The results presented below represent the intent-to-treat population studied in AZA-AML-001 (see section 4.1 for the approved indication).

The efficacy and safety of Vidaza was studied in an international, multicentre, controlled, open-label, parallel group Phase 3 study in patients 65 years and older with newly diagnosed de novo or secondary AML with >30% bone marrow blasts according to the WHO classification, who were not eligible for HSCT. Vidaza plus BSC (n=241) was compared to CCR. CCR consisted of BSC alone (n=45), low-dose cytarabine plus BSC (n=158), or standard intensive chemotherapy with cytarabine and anthracycline plus BSC (n=44). Patients were pre-selected by their physician to 1 of the 3 CCRs prior to randomization. Patients received the pre-selected regimen if not randomised to Vidaza. As part of the inclusion criteria, patients were required to have an ECOG performance status of 0-2 and intermediate- or poor-risk cytogenetic abnormalities. The primary endpoint of the study was overall survival.

Vidaza was administered at a SC dose of 75mg/m^2/day for 7 days, followed by a rest period of 21 days (28 day treatment cycle), for a median of 6 cycles (range: 1 to 28), BSC- only patients for a median of 3 cycles (range: 1 to 20), low-dose cytarabine patients for a median of 4 cycles (range 1 to 25) and standard intensive chemotherapy patients for a median of 2 cycles (range: 1 to 3, induction cycle plus 1 or 2 consolidation cycles).

The individual baseline parameters were comparable between the Vidaza and CCR groups. The median age of the subjects was 75.0 years (range: 64 to 91 years), 75.2% were Caucasian and 59.0% were male. At baseline 60.7% were classified as AML not otherwise specified, 32.4% AML with myelodysplasia-related changes, 4.1% therapy-related myeloid neoplasms and 2.9% AML with recurrent genetic abnormalities according to the WHO classification.

In the ITT analysis of 488 patients (241 Vidaza and 247 CCR), Vidaza treatment was associated with a median survival of 10.4 months versus 6.5 months for those receiving CCR treatment, a difference of 3.8 months, with a stratified log-rank p-value of 0.1009 (two- sided). The hazard ratio for the treatment effect was 0.85 (95% CI= 0.69, 1.03). The one-year survival rates were 46.5% in patients receiving Vidaza versus 34.3% in patients receiving CCR.



The Cox PH model adjusted for pre-specified baseline prognostic factors defined a HR for Vidaza versus CCR of 0.80 (95% CI= 0.66, 0.99; p = 0.0355).

In addition, although the study was not powered to demonstrate a statistically significant difference when comparing azacitidine to the preselection CCR treatment groups, the survival of Vidaza treated patients was longer when compared to CCR treatment options BSC alone, low-dose cytarabine plus BSC and were similar when compared to standard intensive chemotherapy plus BSC.

In all pre- specified subgroups age [(< 75 years & ≥ 75 years), gender, race, ECOG performance status (0 or 1 & 2) , baseline cytogenetic risk (intermediate & poor) , geographic region, WHO classification of AML (including AML with myelodysplasia-related changes), baseline WBC count (≤ 5 x10^9/L & >5 x 10^9/L), baseline bone marrow blasts (≤ 50% & > 50%) and prior history of MDS] there was a trend in OS benefit in favour of Vidaza. In a few pre-specified subgroups, the OS HR reached statistical significance including patients with poor cytogenetic risk, patients with AML with myelodysplasia-related changes, patients < 75 years, female patients and white patients.

Haematologic and cytogenetic responses were assessed by the investigator and by the IRC with similar results. Overall response rate (complete remission [CR] + complete remission with incomplete blood count recovery [CRi]) as determined by the IRC was 27.8% in the Vidaza group and 25.1% in the combined CCR group (p = 0.5384). In patients who achieved CR or CRi, the median duration of remission was 10.4 months (95% CI = 7.2, 15.2) for the Vidaza subjects and 12.3 months (95% CI = 9.0, 17.0) for the CCR subjects. A survival benefit was also demonstrated in patients that had not achieved a complete response for Vidaza compared to CCR.

Vidaza treatment improved peripheral blood counts and led to a reduced need for RBC and platelet transfusions. A patient was considered RBC or platelet transfusion dependent at baseline if the subject had one or more RBC or platelet transfusions during the 56 days (8 weeks) on or prior to randomization, respectively. A patient was considered RBC or platelet transfusion independent during the treatment period if the subject had no RBC or platelet transfusions during any consecutive 56 days during the reporting period, respectively.

Of the patients in the Vidaza group who were RBC transfusion dependent at baseline, 38.5% (95% CI = 31.1, 46.2) of these patients became RBC transfusion independent during the treatment period, compared with 27.6% of (95% CI = 20.9, 35.1) patients in the combined CCR groups. In patients who were RBC transfusion dependent at baseline and achieved transfusion independence on

treatment, the median duration of RBC transfusion independence was 13.9 months in the Vidaza group and was not reached in the CCR group.

Of the patients in the Vidaza group who were platelet transfusion dependent at baseline, 40.6% (95% CI = 30.9, 50.8) of these patients became platelet transfusion independent during the treatment period, compared with 29.3% of (95% CI = 19.7, 40.4) patients in the combined CCR groups. In patients who were platelet transfusion dependent at baseline and achieved transfusion independence on treatment, the median duration of platelet transfusion independence was 10.8 months in the Vidaza group and 19.2 months in the CCR group.

Health- Related Quality of Life (HRQoL) was assessed using the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30). HRQoL data could be analysed for a subset of the full trial population. While there are limitations in the analysis, the available data suggest that patients do not experience meaningful deterioration in quality of life during treatment with Vidaza.

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 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 4.4).

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:
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 Special precautions for storage

Unopened vials
This medicinal product does not require any special storage conditions.

Reconstituted suspension
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 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

6.6 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
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 medicinal product 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. 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 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. 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 45-90° 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
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/488/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 December 2008
Date of latest renewal: 17 December 2013

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Baxter Oncology GmbH
Kantstrasse 2
33790 Halle/Westfalen
Germany

Celgene Europe Ltd
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Vidaza 25 mg/mL powder for suspension for injection
Azacitidine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains100 mg azacitidine. After reconstitution, each mL suspension contains 25 mg azacitidine.

3. LIST OF EXCIPIENTS

Also contains mannitol.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for suspension for injection.
1 vial – 100 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For single use only. Shake the suspension vigorously before administration.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic

8. EXPIRY DATE

EXP

Read the leaflet for the shelf life of the reconstituted medicine.

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused product or waste material should be discarded according to the local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Celgene Europe Ltd
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/488/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Vidaza 25 mg/mL powder for suspension for injection
Azacitidine
Subcutaneous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 mg

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Vidaza 25 mg/mL powder for suspension for injection
Azacitidine

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:
1. What Vidaza is and what it is used for
2. What you need to know before you use Vidaza
3. How to use Vidaza
4. Possible side effects
5 How to store Vidaza
6. Contents of the pack and other information

1. What Vidaza is and what it is used for

What Vidaza is
Vidaza is an anti-cancer agent which belongs to a group of medicines called ‘anti-metabolites’. Vidaza contains the active substance ‘azacitidine’.

What Vidaza is used for
Vidaza is used in adults who are not able to have a stem cell transplantation to treat:
- higher-risk myelodysplastic syndromes (MDS).
- chronic myelomonocytic leukaemia (CMML).
- acute myeloid leukaemia (AML).

These are diseases which affect the bone marrow and can cause problems with normal blood cell production.

How Vidaza works
Vidaza works by preventing cancer cells from growing. Azacitidine becomes incorporated into the genetic material of cells (ribonucleic acid (RNA) and deoxyribonucleic acid (DNA)). It is thought to work by altering the way the cell turns genes on and off and also by interfering with the production of new RNA and DNA. These actions are thought to correct problems with the maturation and growth of young blood cells in the bone marrow that cause myelodysplastic disorders, and to kill cancerous cells in leukaemia.
Talk to your doctor or nurse if you have any questions about how Vidaza works or why this medicine has been prescribed for you.

2. What you need to know before you use Vidaza

Do not use Vidaza
- if you are allergic to azacitidine or any of the other ingredients of this medicine (listed in section 6).
- if you have advanced liver cancer.
- if you are breast-feeding.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Vidaza in the following situations:
- if you have decreased counts of platelets, red or white blood cells.
- if you have kidney disease.
- if you have liver disease.
- if you have ever had a heart condition or heart attack or any history of lung disease.

Blood test
You will have blood tests before you begin treatment with Vidaza and at the start of each period of treatment (called a 'cycle'). This is to check that you have enough blood cells and that your liver and kidneys are working properly.

Children and adolescents
Vidaza is not recommended for use in children and adolescents below the age of 18.

Other medicines and Vidaza
Tell your doctor, pharmacist or nurse if you are using or have recently used any other medicines. This is because Vidaza may affect the way some other medicines work. Also, some other medicines may affect the way Vidaza works.

Pregnancy
You should not use Vidaza during pregnancy as it may be harmful to the baby.
Use an effective method of contraception during and up to 3 months after treatment.
Tell your doctor straight away if you become pregnant during treatment.

If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Breast-feeding
You should not breast-feed when using Vidaza. It is not known if this medicine passes into human milk.

Fertility
Men should not father a child while receiving treatment with Vidaza. Use an effective method of contraception during and up to 3 months after treatment with this medicine.

Talk to your doctor if you wish to conserve your sperm before starting this treatment.

Driving and using machines
Do not drive or use any tools or machines if you experience side effects, such as tiredness.

3. How to use Vidaza

Before giving you Vidaza, your doctor will give you another medicine to prevent nausea and vomiting at the start of each treatment cycle.

- The recommended dose is 75 mg per m^2 body surface area. Your doctor will decide your dose of this medicine, depending on your general condition, height and weight. Your doctor will check your progress and may change your dose if necessary.
- Vidaza is given every day for one week, followed by a rest period of 3 weeks. This "treatment cycle" will be repeated every 4 weeks. You will usually receive at least 6 treatment cycles.

This medicine will be given to you as an injection under the skin (subcutaneously) by a doctor or nurse. It may be given under the skin on your thigh, tummy or upper arm.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor straight away if you notice any of the following side effects:

- **Drowsiness, shaking, jaundice, abdominal bloating and easy bruising**. These may be symptoms of liver failure and can be life-threatening.
- **Swelling of the legs and feet, back pain, reduced passing of water, increased thirst, rapid pulse, dizziness and nausea, vomiting or reduced appetite and feelings of confusion, restlessness or fatigue.** These may be symptoms of kidney failure and can be life-threatening.
- **A fever**. This could be due to an infection as a result of having low levels of white blood cells, which can be life-threatening.
- **Chest pain or shortness of breath which may be accompanied with a fever.** This may be due to an infection of the lung called "pneumonia", and can be life-threatening.
- **Bleeding.** Such as blood in the stools due to bleeding in the stomach or gut, or such as bleeding inside your head. These may be symptoms of having low levels of platelets in your blood.
- **Difficulty breathing, swelling of the lips, itching or rash.** This may be due to an allergic (hypersensitivity) reaction.

Other side effects include:

Very common side effects (may affect more than 1 in 10 people)

- Reduced red blood count (anaemia). You may feel tired and pale.
- Reduced white blood cell count. This may be accompanied by a fever. You are also more likely to get infections.
- A low blood platelet count (thrombocytopenia). You are more prone to bleeding and bruising.
- Constipation, diarrhoea, nausea, vomiting.
- Pneumonia.
- Chest pain, being short of breath.
- Tiredness (fatigue).
- Injection site reaction including redness, pain or a skin reaction.
- Loss of appetite.
- Joint aches.
- Bruising.
- Rash.
- Red or purple spots under your skin.
- Pain in your belly (abdominal pain).
- Itching.
- Fever.
- Sore nose and throat.
- Dizziness.
- Headache.
- Having trouble sleeping (insomnia).
- Nosebleeds (epistaxis).
- Muscle aches.
- Weakness (asthenia).
- Weight loss.
- Low levels of potassium in your blood.

Common side effects (may affect up to 1 in 10 people)

- Bleeding inside your head.
- An infection of the blood caused by bacteria (sepsis). This may be due to low levels of white cells in your blood.

- Bone marrow failure. This can cause low levels of red and white blood cells and platelets.
- A type of anaemia where your red and white blood cells and platelets are reduced.
- An infection in your urine.
- A viral infection causing cold sores (herpes).
- Bleeding gums, bleeding in the stomach or gut, bleeding from around your back passage due to piles (haemorrhoidal haemorrhage), bleeding in your eye, bleeding under your skin, or into your skin (haematoma).
- Blood in your urine.
- Ulcers of your mouth or tongue.
- Changes to your skin at the injection site. These include swelling, a hard lump, bruising, bleeding into your skin (haematoma), rash, itching and changes in the skin colour.
- Redness of your skin.
- Skin infection (cellulitis).
- An infection of the nose and throat, or sore throat.
- Sore or runny nose or sinuses (sinusitis)..
- High or low blood pressure (hypertension or hypotension).
- Being short of breath when you move.
- Pain in your throat and voicebox.
- Indigestion.
- Lethargy.
- Feeling generally unwell.
- Anxiety.
- Being confused.
- Hair loss.
- Kidney failure.
- Dehydration.
- White coating covering tongue, inner cheeks, and sometimes on the roof of your mouth, gums and tonsils (oral fungal infection).
- Fainting.
- A fall in blood pressure when standing (orthostatic hypotension) leading to dizziness when moving to a standing or sitting position.
- Sleepiness, drowsiness (somnolence).
- Bleeding due to a catheter line.
- A disease affecting the gut which can result in fever, vomiting and stomach pain (diverticulitis).
- Fluid around the lungs (pleural effusion).
- Shivering (chills).
- Muscle spasms.
- Raised itchy rash on the skin (urticaria).

Uncommon side effects (may affect up to 1 in 100 people)
- Allergic (hypersensitivity) reaction.
- Shaking.
- Liver failure.
- Large plum-coloured, raised painful patches on the skin with fever.
- Painful skin ulceration (pyoderma gangrenosum).

Rare side effects (may affect up to 1 in 1,000 people)
- Dry cough.
- Painless swelling in the finger tips (clubbing).
- Tumour lysis syndrome - Metabolic complications that can occur during treatment of cancer and sometimes even without treatment. These complications are caused by the product of dying cancer cells and may include the following: changes to blood chemistry; high potassium, phosphorus, uric acid, and low calcium consequently leading to changes in kidney function, heartbeat, seizures, and sometimes death.

Not known (frequency cannot be estimated from the available data)

- Infection of the deeper layers of skin, which spreads quickly, damaging the skin and tissue, which can be life-threatening (necrotizing fasciitis).

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Vidaza

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial label and the carton. The expiry date refers to the last day of that month.

Your doctor, pharmacist or nurse are responsible for storing Vidaza. They are also responsible for preparing and disposing of any unused Vidaza correctly.

For unopened vials of this medicine – there are no special storage conditions.

When using immediately
Once the suspension has been prepared it should be administered within 45 minutes.

When using later on
If the Vidaza suspension is prepared using water for injections that has not been refrigerated, the suspension must be placed in the refrigerator (2 °C – 8 °C) immediately after it is prepared and kept refrigerated for up to a maximum of 8 hours.
If the Vidaza suspension is prepared using water for injections that has been stored in the refrigerator (2 °C – 8 °C), the suspension must be placed in the refrigerator (2 °C – 8 °C) immediately after it is prepared and kept refrigerated for up to a maximum of 22 hours.

The suspension should be allowed up to 30 minutes prior to administration to reach room temperature (20 °C – 25 °C).

If large particles are present in the suspension it should be discarded.

6. Contents of the pack and other information

What Vidaza contains

- The active substance is azacitidine. One vial contains 100 mg azacitidine. After reconstitution with 4 mL of water for injections, the reconstituted suspension contains 25 mg/mL azacitidine.
- The other ingredient is mannitol (E421).

What Vidaza looks like and contents of the pack
Vidaza is a white powder for suspension for injection and is supplied in a glass vial containing 100 mg of azacitidine. Each pack contains one vial of Vidaza.

Marketing Authorisation Holder and Manufacturer
Celgene Europe Ltd
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom
OR
Marketing Authorisation Holder
Celgene Europe Ltd
1 Longwalk Road
Stockley Park
Uxbridge
UB11 1DB
United Kingdom

Manufacturer
Baxter Oncology GmbH
Kantstrasse 2
33790 Halle/Westfalen
Germany

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

The following information is intended for healthcare professionals only:

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.

Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned below (see “Reconstitution Procedure”).

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 medicinal product 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. 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 ºC-25 ºC. 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 immediate use

The Vidaza suspension may 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.

For later use

When reconstituting using water for injections that has not been refrigerated, the reconstituted suspension 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.

When reconstituting using refrigerated (2 °C to 8 °C) water for injections, the reconstituted suspension must be placed in a refrigerator (2 °C to 8 °C) immediately after reconstitution, and kept in a refrigerator for a maximum of 22 hours. If the elapsed time in the refrigerator is greater than 22 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 ºC-25 ºC. 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:

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
Do not filter the suspension after reconstitution.

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.

Annex IV

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR for azacitidine, the scientific conclusions of CHMP are as follows:

Scientific conclusions and grounds for variation to the terms of the marketing authorisations

During the reporting interval, there were 3 new reports of pyoderma gangrenosum, and 13 reports have been received cumulatively. Taking into account all sources of information (studies, literature, spontaneous reports), 20 reports of azacitidine-associated pyoderma gangrenosum were retrieved from the safety database. Among these, there were 3 biopsy-confirmed cases with a positive rechallenge and three cases reporting a positive dechallenge, although only one was confirmed by biopsy. Overall, the cumulative data received to date, and in particular the 3 cases with a positive rechallenge, indicate that treatment with azacitidine is associated with the risk of pyoderma gangrenosum. Pyoderma gangrenosum should therefore be included as an adverse drug reaction in the summary of product characteristics of azacitidine with a frequency “uncommon”. The package leaflet should be updated accordingly.

Cumulatively, 16 cases of tumour lysis syndrome have been reported to date, of which 7 during post-marketing experience. The cumulative data indicates that, even though patients initiating azacitidine are at risk of developing tumour lysis syndrome, the overall risk appears to be low. This is further supported by the finding that no cases of tumour lysis syndrome have occurred in marketing authorisation holder-sponsored studies. Currently tumour lysis syndrome is addressed in section 4.8 of the summary of product characteristics (frequency: rare), and listed as important identified risk in the risk management plan. The PRAC endorsed the MAH proposal to include an additional warning on tumour lysis syndrome in section 4.4 of the summary of product characteristics.

Therefore, in view of the data presented in the reviewed PSUR(s), the PRAC considered that changes to the product information of medicinal products containing azacitidine were warranted.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for azacitidine the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing azacitidine is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the Marketing Authorisation(s) should be varied.