SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

VIDAZA (Powder for suspension for Injection)

COMPOSITION

Each vial contains 100 mg azacitidine. The reconstituted suspension contains 25 mg/ml azacitidine.

PHARMACOLOGICAL CLASSIFICATION

A 26 – Cytostatics

PHARMACOLOGICAL ACTION

Pharmacodynamics

Azacitidine is believed to exert its antineoplastic effects by causing hypomethylation of DNA and direct cytotoxicity on abnormal haematopoietic cells in the bone marrow. The concentration of azacitidine required for maximum inhibition of DNA methylation *in vitro* does not cause major suppression of DNA synthesis. Hypomethylation may restore normal function to genes that are critical for differentiation and proliferation. The cytotoxic effects of azacitidine cause the death of rapidly dividing cells including cancer cells that are no longer responsive to normal growth control mechanisms. Non-proliferating cells are relatively insensitive to azacitidine.

Pharmacokinetics

The pharmacokinetics of azacitidine were studied in six MDS patients following a single 75 mg/m^2 SC and a single 75 mg/m^2 intravenous (IV) dose. Azacitidine was rapidly absorbed after SC administration: the peak plasma azacitidine concentration of 750 ±

403 ng/mL occurred in 0,5 hour. The bioavailability of SC azacitidine relative to IV azacitidine was approximately 89 % based on area under the curve. Mean volume of distribution following IV dosing was 76 ± 26 l. Mean apparent SC clearance was 167 ± 49 l/hr, and mean half-life after SC administration was 41 ± 8 minutes.

An *in vitro* study of azacitidine incubation in human liver fractions indicated that azacitidine may be metabolised by the liver. Whether azacitidine metabolism may be affected by known microsomal enzyme inhibitors or inducers has not been studied. *In vitro* studies of azacitidine with human cultured hepatocytes indicate that azacitidine at concentrations of 1,0 µM to 100 µM does not induce CYP 1A2, 2C19, or 3A4/5.

Published studies indicate that urinary excretion is the primary route of elimination of azacitidine and its metabolites. Following IV administration of radioactive azacitidine to 5 cancer patients, the cumulative urinary excretion was 85 % of the radioactive dose. Faecal excretion accounted for < 1 % of administered radioactivity over three days. Mean excretion of radioactivity in urine following SC administration of ^{14}C-azacitidine was 50 %. The mean elimination half-lives of total radioactivity (azacitidine and its metabolites) were similar after IV and SC administrations, about 4 hours.

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

INDICATIONS

Vidaza™ is indicated for treatment of patients with myelodysplastic syndromes including the following subtypes of the French–American–British classification: refractory anaemia or refractory anaemia with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anaemia with excess blasts, refractory anaemia with excess blasts in transformation, and chronic myelomonocytic leukaemia.

CONTRA-INDICATIONS

Vidaza™ is contraindicated in the following:

- patients with known hypersensitivity to Vidaza™ (azacitidine) or to any of the excipients.
- patients with advanced malignant hepatic tumours.

WARNINGS

Haematological toxicity

Treatment with Vidaza™ is associated with anaemia, neutropenia and thrombocytopenia, particularly during the first 2 cycles. Complete blood counts should be performed as needed to monitor response and toxicity, but at least prior to each treatment cycle. Patients should be advised to promptly report febrile episodes. Patients and physicians are also advised to be observant for signs and symptoms of bleeding. (See 'SPECIAL PRECAUTIONS')

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 Vidaza™ treatment, especially in such patients with baseline serum albumin < 30 g/l. Azacitidine is contraindicated in patients with advanced malignant hepatic tumours. (See 'SPECIAL PRECAUTIONS')

Renal impairment

Renal abnormalities ranging from elevated serum creatinine to renal failure and death were reported in patients treated with Vidaza™ 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. (See 'SPECIAL PRECAUTIONS')

INTERACTIONS

Medicine interaction studies with Vidaza™ have not been conducted.
An *in vitro* study of Vidaza™ incubation in human liver fractions indicated that Vidaza™ may be metabolised by the liver. Whether Vidaza™ metabolism may be affected by known microsomal enzyme inhibitors or inducers has not been studied.
In vitro studies of Vidaza™ with human cultured hepatocytes indicate that Vidaza™ at concentrations of 1,0 µM to 100 µM does not induce CYP 1A2, 2C19, or 3A4/5.
The potential of Vidaza™ to inhibit cytochrome P450 (CYP) enzymes is not known.

PREGNANCY AND LACTATION

Pregnancy:

Safety in pregnancy and lactation has not been established.

Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with Vidaza™.

There are no adequate data on the use of Vidaza™ in pregnant women. Studies in animals have shown reproductive toxicity. The potential risk for humans is unknown. Vidaza™ should not be used during pregnancy.

If the patient becomes pregnant while taking Vidaza™, the patient should be informed of the potential hazard to the fetus.

Lactation:

It is not known whether Vidaza™ or its metabolites are excreted in human milk. Because of the potential for tumorigenicity shown for Vidaza™ in animal studies and the potential for serious adverse reactions, women treated with Vidaza™ should not breast feed.

DOSAGE AND DIRECTIONS FOR USE

The recommended starting dose is 75 mg/m^2 subcutaneously, daily for seven days, every four weeks. Patients should be premedicated for nausea and vomiting. The dose may be increased to 100 mg/m^2 if no beneficial effect is seen after two treatment cycles and if no toxicity other than nausea and vomiting has occurred. It is recommended that patients be treated for a minimum of 4 cycles. However, complete or partial response may require more than 4 treatment cycles. Treatment may be continued as long as the patient continues to benefit.

Patients should be monitored for haematologic response and renal toxicities, and dosage delay or reduction as described below may be necessary.

Dosage Adjustment based on Haematology Laboratory Values:

- For patients with baseline (start of treatment) WBC ≥ 3,0 x10^9/l, ANC ≥ 1,5 x10^9/l, and platelets ≥ 75,0 x10^9/l, adjust the dose as follows, based on nadir counts for any given cycle:

Nadir Counts		% Dose in the Next Course
ANC (x10^9/l)	Platelets (x10^9/l)	
< 0,5	< 25,0	50 %
0,5 –1,5	25,0 - 50,0	67 %
> 1,5	> 50,0	100 %

- For patients whose baseline counts are WBC < 3,0 x10^9/l, ANC < 1,5 x10^9/l, or platelets < 75,0 x10^9/l, dose adjustments should be based on nadir counts and bone marrow biopsy cellularity at the time of the nadir as noted below, unless there is clear improvement in differentiation (percentage of mature granulocytes is higher and ANC is higher than at onset of that course) at the time of the next cycle, in which case the dose of the current treatment should be continued.

WBC or Platelet Nadir % decrease in counts from baseline	Bone Marrow Biopsy Cellularity at Time of Nadir (%)		
	30 - 60	15 - 30	< 15
	% Dose in the Next Course		
50 - 75	100	50	33
> 75	75	50	33

Dosage Adjustment Based on Renal Function and Serum Electrolytes: If unexplained elevations of serum creatinine or blood urea 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 course. Similarly, if unexplained reductions in serum bicarbonate levels to less than 20 mmol/l occur, the dosage should be reduced by 50 % on the next course.

Special Populations:

Patients with Renal Impairment: No studies have been conducted in MDS patients with decreased renal function. Since Vidaza™ and its metabolites are primarily excreted by the kidneys, patients with renal impairment should be monitored closely and the dose adjusted as described.

Patients with Hepatic Impairment: No studies have been conducted in MDS patients with hepatic impairment. Since Vidaza™ may be metabolised in the liver and is potentially hepatotoxic in patients with severe pre-existing hepatic impairment caution is needed in patients with liver disease.

Elderly: Vidaza™ and its metabolites are known to be substantially excreted by the kidney, and the risk of toxic reactions to Vidaza™ may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Children: The safety and efficacy of Vidaza™ in children and adolescents under 18 years of age has not been established.

Laboratory Tests

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

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

Administration:

Vidaza™ should be administered under the supervision of a medical practitioner qualified in the use of anticancer agents.

Reconstituted Vidaza™ should be injected subcutaneously.

Rotate sites for injection (thigh, abdomen, or upper arm). New injections should be given at least one inch from an old site and never into areas were the site is tender, bruised, red, or hard.

Recommendations for safe handling:

Vidaza™ is a cytotoxic medicine and caution should be exercised when handling and preparing Vidaza™ suspensions. Procedures for proper handling and disposal of anticancer medicines should be applied.

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

Preparation for the subcutaneous administration: Vidaza™ should be reconstituted aseptically with 4 ml sterile water for injection. The diluent should be injected slowly into the vial. Vigorously shake or roll the vial until a uniform suspension is achieved. The suspension will be cloudy. The resulting suspension will contain azacitidine 25 mg/ml.
When stored at 25 ºC, the reconstituted product should be administered within 1 hour. Doses greater than 4 ml should be divided equally into two syringes and injected into two separate sites. To provide a homogeneous suspension, the contents of the syringe must be re-suspended by inverting the syringe 2–3 times and vigorously rolling the syringe between the palms for 30 seconds immediately prior to administration.
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.

Preparation for delayed administration: The reconstituted product may be kept in the vial or drawn into a syringe. The product must be refrigerated (2 ºC – 8 ºC) immediately. After removal from refrigerated conditions, the suspension may be allowed to equilibrate to room temperature (25 ºC) for up to 30 minutes prior to administration.

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

SIDE EFFECTS AND SPECIAL PRECAUTIONS

Side-effects:

The most commonly reported adverse reactions were gastrointestinal (nausea, vomiting and diarrhoea), haematological (anaemia, thrombocytopenia, leukopenia/neutropenia), and injection site reactions (erythema and pain). In general, these events reflect the underlying nature of the disease and that Vidaza™ is cytotoxic. No clinically significant differences were seen when the safety data were analysed for age, gender or MDS subtypes.

Adverse reactions reported in more than an isolated case are listed below in patients treated with SC Vidaza™ in clinical studies (N=220), by system organ class (alphabetically) and by frequency (alphabetically by MedDRA preferred term). Frequencies are defined as: very common (≥1/10), common (≥1/100, ≤ 1/10), uncommon (≥1/1000, < 1/100), rare (< 1/1000). Since the frequencies are based on 220 patients, none of the reactions were categorized as rare (0,1 %) as an occurrence in 1 patient represented a 0,45 % frequency. Reactions included in the table are adverse events occurring in Vidaza™ -treated patients at a frequency of at least twice that observed in the supportive care only (observation) group; all reactions categorized as uncommon were reported in 2 Vidaza™ -treated patients (0,9 %; 2/220) and were not reported in the observation group (N=92).

System Organ Class	Very Common (≥1/10)	Common (≥1/100, < 1/10)	Uncommon (≥1/1000, < 1/100)
Blood and lymphatic system disorders	anaemia, febrile neutropenia, leukopenia, neutropenia, thrombocytopenia	lymphadenopathy	agranulocytosis
Gastrointestinal disorders	constipation, diarrhoea, nausea, vomiting	gastrointestinal haemorrhage, gingival bleeding, loose stools, oral mucosal petechiae, stomatitis, tongue ulceration	perirectal abscess
General disorders and administrative site conditions	chest pain, fatigue aggravated, injection site bruising, injection site erythema, injection site pain, injection site	injection site granuloma, injection site pigmentation changes, injection site swelling, lethargy	

System Organ Class	Very Common (≥1/10)	Common (≥1/100, < 1/10)	Uncommon (≥1/1000, < 1/100)
	reaction, malaise, rigors		
Immune system disorders		drug hypersensitivity	
Infections and infestations	nasopharyngitis, pneumonia, upper respiratory tract infection	bacterial infection,	
Injury, poisoning and procedural complications		post procedural haemorrhage	
Investigations		blood creatinine increased	
Metabolic and nutrition disorders	Anorexia		
Musculoskeletal, and connective tissue disorders	arthralgia, myalgia,		
Nervous system disorders	Dizziness	burning sensation, hypoaesthesia, intra-cranial haemorrhage	
Psychiatric disorders	anxiety, insomnia		
Renal and urinary disorders		dysuria	
Respiratory, thoracic and mediastinal disorders	dyspnoea, pharyngitis,	haemoptysis, nasal congestion	

System Organ Class	Very Common (≥1/10)	Common (≥1/100, < 1/10)	Uncommon (≥1/1000, < 1/100)
Skin and subcutaneous tissue disorders	ecchymosis, erythema, increased sweating rash	pruritic rash, urticaria	
Vascular disorders	petechiae	flushing, haematoma	

Special Precautions

Men should be advised not to father a child while receiving treatment with Vidaza™.

Treatment with Vidaza™ is associated with neutropenia and thrombocytopenia. Complete blood counts should be performed as needed to monitor response and toxicity, but at a minimum, prior to each dosing cycle. After administration of the recommended dosage for the first cycle, dosage for subsequent cycles should be reduced or delayed based on nadir counts and haematologic response as described in Dosage and directions for use.

Safety and effectiveness of Vidaza™ in patients with MDS and hepatic or renal impairment have not been studied.

Because Vidaza™ is potentially hepatotoxic in patients with severe pre-existing hepatic impairment, caution is needed in patients with liver disease. Patients with extensive tumour burden due to metastatic disease have been rarely reported to experience progressive hepatic coma and death during Vidaza™ treatment, especially in such patients with baseline albumin <30 g/l. Vidaza™ is contraindicated in patients with advanced malignant hepatic tumours.

Renal abnormalities ranging from elevated serum creatinine to renal failure and death were reported in patients treated with intravenous (IV) Vidaza™ in combination with other chemotherapeutic agents for non-MDS conditions. 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 CML treated with Vidaza™ and etoposide. If unexplained elevations of serum creatinine or blood urea or reductions in serum bicarbonate (< 20 mmol/l) occur, the dosage should be reduced or held as described in 'DOSAGE AND DIRECTIONS FOR USE'.

Patients with renal impairment should be closely monitored for toxicity since Vidaza™ and its metabolites are primarily excreted by the kidney.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

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

One case of overdose with Vidaza™ was reported during clinical trials. A patient experienced diarrhoea, nausea, and vomiting after receiving a single IV dose of approximately 290 mg/m^2, almost 4 times the recommended starting dose. The events resolved without sequelae, and the correct dose was resumed the following day.

IDENTIFICATION

White to off-white, sterile lyophilised powder.

PRESENTATION

Colourless single use Type I glass vial sealed with a grey butyl rubber stopper and aluminium seal with plastic button.

STORAGE INSTRUCTIONS

Powder for injection: Store below 25 °C.

After reconstitution: Reconstituted Vidaza™ may be stored for up to 8 hours between 2 °C and 8 °C.

If administration is to be delayed, the reconstituted product may be kept in the vial or drawn into a syringe. The product must be refrigerated (2 ºC – 8 ºC) immediately. After removal from refrigerated conditions, the suspension may be allowed to equilibrate to room temperature (25 ºC) for up to 30 minutes prior to administration.

When stored at 25 ºC, the reconstituted product should be administered within 1 hour.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

A40/26/0521

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