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 antiinfectives 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.

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.

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.

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.

Elderly population

There is limited safety information available with azacitidine in patients ⩾ 85 years

OVERDOSE

One case of overdose with Azacitidine for Injection was reported during clinical trials. A patient experienced diarrhea, 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. 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 Azacitidine overdosage

PHARMACOLOGICAL PROPERTIES

Pharmacodynamics

Pharmacotherapeutic group: Antineoplastic agent, pyrimidine analogues; ATC code: L01BC07

Mechanism of Action

Azacitidine is a pyrimidine nucleoside analog of cytidine. AZACITIDINE is believed to exert its antineoplastic effects by causing hypomethylation of DNA and direct cytotoxicity on abnormal hematopoietic 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 6 MDS patients following a single 75 mg/m^2 subcutaneous (SC) dose and a single 75 mg/m^2 intravenous (IV) dose. Azacitidine is 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 is approximately 89%, based on area under the curve. Mean volume of distribution following IV dosing is 76 ± 26 L. Mean apparent SC clearance is 167 ± 49 L/hour and mean half-life after SC administration is 41 ± 8 minutes. The AUC and Cmax of SC administration of azacitidine in 21 patients with cancer were approximately dose proportional within the 25 to 100 mg/m^2 dose range. Multiple dosing at the recommended dose-regimen does not result in drug accumulation

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. Fecal excretion accounted for <1% of administered radioactivity over 3 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.

INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products including 5% Dextrose solutions, Hespan, or solutions that contain bicarbonate. These solutions have the potential to increase the rate of degradation of Azacitidine and should therefore be avoided.

STORAGE CONDITION

Store at a temperature not exceeding 25°C.

In Use Stability

S.C. Suspension Stability: AZACITIDINE reconstituted with non-refrigerated water for injection for subcutaneous administration may be stored for up to 1 hour at 25°C (77°F) or for up to 8 hours between 2°C and 8°C (36°F and 46°F); when reconstituted with refrigerated (2°C - 8°C, 36°F - 46°F) water for injection, it may be stored for 22 hours between 2°C and 8°C (36°F and 46°F).

I.V. Solution Stability: AZACITIDINE reconstituted for intravenous administration may be stored at 25°C (77°F), but administration must be completed within 1 hour of reconstitution.

INSTRUCTION FOR USE AND HANDLING

Azacitidine is a cytotoxic drug. Follow applicable special handling and disposal procedures.

Instruction for Subcutaneous Administration

Reconstitute AZACITIDINE aseptically with 4 mL sterile water for injection. Inject the diluent 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. Do not filter the suspension after reconstitution. Doing so could remove the active substance.

Preparation for Immediate Subcutaneous Administration: Doses greater than 4 mL should be divided equally into 2 syringes. The product may be held at room temperature for up to 1 hour, but must be administered within 1 hour after reconstitution.

Preparation for Delayed Subcutaneous Administration: The reconstituted product may be kept in the vial or drawn into a syringe. Doses greater than 4 mL should be divided equally into 2 syringes. The product must be refrigerated immediately. When AZACITIDINE is reconstituted using water for injection that has not been refrigerated, the reconstituted product may be

held under refrigerated conditions (2°C - 8°C, 36°F - 46°F) for up to 8 hours. When AZACITIDINE is reconstituted using refrigerated (2°C - 8°C, 36°F - 46°F) water for injection, the reconstituted product may be stored under refrigerated conditions (2°C - 8°C, 36°F - 46°F) for up to 22 hours. After removal from refrigerated conditions, the suspension may be allowed to equilibrate to room temperature for up to 30 minutes prior to administration.

Subcutaneous Administration

To provide a homogeneous suspension, the contents of the dosing syringe must be re-suspended immediately prior to administration. To re-suspend, vigorously roll the syringe between the palms until a uniform, cloudy suspension is achieved.

AZACITIDINE suspension is administered subcutaneously. Doses greater than 4 mL should be divided equally into 2 syringes and injected into 2 separate sites. Rotate sites for each injection (thigh, abdomen, or upper arm). New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, red, or hard.

Instructions for Intravenous Administration

Reconstitute the appropriate number of AZACITIDINE vials to achieve the desired dose. Reconstitute each vial with 10 mL sterile water for injection. Vigorously shake or roll the vial until all solids are dissolved. The resulting solution will contain azacitidine 10 mg/mL. The solution should be clear. Parenteral drug product should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Withdraw the required amount of AZACITIDINE solution to deliver the desired dose and inject into a 50 -100 mL infusion bag of either 0.9% Sodium Chloride Injection or Lactated Ringer's Injection.

Intravenous Administration

AZACITIDINE solution is administered intravenously. Administer the total dose over a period of 10 - 40 minutes. The administration must be completed within 1 hour of reconstitution of the AZACITIDINE vial.

EFFECT ON ABILITY TO DRIVE AND USE MACHINE

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

PACKAGING

Azacitidine for injection is supplied as a lyophilized powder in 100 mg single-dose vials packaged in unit carton

MA HOLDER AND MANUFACTURER

Getwell Pharmaceuticals
474 Udyog Vihar, Phase V
Gurgaon 122016, Haryana, INDIA

10/2016

If in doubt do not hesitate to seek advice from your doctor or pharmacist

0709AAGE0117-00

GETWELL

For the use of Registered Medical Practitioner or Hospital or a Laboratory only.

Azacitidine for Injection 100mg

AZACITE™

Lyophilized
Single Dose Vial
For Subcutaneous and Intravenous Use Only

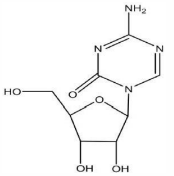
Rx only

WARNING

- Anemia, Neutropenia and Thrombocytopenia: Monitor complete blood counts (CBC) frequently.
- Hepatotoxicity: Patients with severe preexisting hepatic impairment are at higher risk for toxicity.
- Renal Toxicity: Monitor patients with renal impairment for toxicity since azacitidine and its metabolites are primarily excreted by the kidneys.
- Tumor Lysis Syndrome: AZACITIDINE may cause fatal or serious tumor lysis syndrome, including in patients with MDS. Assess baseline risk and monitor and treat as appropriate.
- Embryo-Fetal Risk: AZACITIDINE can cause fetal harm. Advise females with reproductive potential of the potential risk to a fetus and to avoid pregnancy.

DESCRIPTION

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



The empirical formula is $C_8H_{12}N_4O_5$. The molecular weight is 244. Azacitidine is a white to off-white solid. Azacitidine was found to be insoluble in acetone, ethanol, and methyl ethyl ketone; slightly soluble in ethanol/water (50/50), propylene glycol, and polyethylene glycol; sparingly soluble in water, water saturated octanol, 5% dextrose in water, N-methyl-2-pyrrolidone, normal saline and 5% Tween 80 in water; and soluble in dimethylsulfoxide (DMSO).

The finished product is supplied in a sterile form for reconstitution as a suspension for subcutaneous injection or reconstitution as a solution with further dilution for intravenous infusion. Vials of Azacitidine for Injection contain 100 mg of azacitidine and 100 mg mannitol as a sterile lyophilized powder

PHARMACEUTICAL FORM, DOSAGE AND ROUTE OF ADMINISTRATION

Pharmaceutical form: Lyophilized powder
Dosage: 100mg/vial
Route of Administration: Subcutaneous or Intravenous

COMPOSITION

Each vial contains:

Azacitidine	100mg
Mannitol USP	100mg
Water for Injection USP	q.s.

THERAPEUTICE INDICATION

Azacitidine is indicated for treatment of patients with the following French-American-British (FAB) myelodysplastic syndrome subtypes: refractory anemia (RA) or refractory anemia with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMMoL).

DOSAGE AND METHOD OF ADMINISTRATION

First Treatment Cycle

The recommended starting dose for the first treatment cycle, for all patients regardless of baseline hematology laboratory values, is 75 mg/m^2 subcutaneously or intravenously, daily for 7 days. Premedicate patients for nausea and vomiting. Obtain complete blood counts, liver chemistries and

serum creatinine prior to the first dose.

Subsequent Treatment Cycles

Repeat cycles every 4 weeks. The dose may be increased to 100 mg/m^2 if no beneficial effect is seen after 2 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 to 6 cycles. However, complete or partial response may require additional treatment cycles. Treatment may be continued as long as the patient continues to benefit.

Monitor patients for hematologic response and renal toxicities and delay or reduce dosage if necessary as described below.

Dosage Adjustment Based on Hematology 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, base dose adjustments 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 continue the current dose.

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 Serum Electrolytes and Renal Toxicity

If unexplained reductions in serum bicarbonate levels to <20 mEq/L occur, reduce the dosage by 50% for the next course. Similarly, if unexplained elevations of BUN or serum creatinine occur, delay the next cycle until values return to normal or baseline and reduce the dose by 50% for the next course.

Use in Geriatric Patients

Azacitidine and its metabolites are known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, select the dose carefully and monitor renal function.

Method of Preparation

Azacitidine is a cytotoxic drug. Procedures for proper handling and disposal of cytotoxic drugs should be considered.

Azacitidine for Injection is a single-dose vial and does not contain any preservatives. Discard unused portions of each vial properly. Do not save any unused portions for later administration.

Instruction for Subcutaneous Administration

Reconstitute AZACITIDINE aseptically with 4 mL sterile water for injection. Inject the diluent 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. Do not filter the suspension after reconstitution. Doing so could remove the active substance.

Preparation for Immediate Subcutaneous Administration: Doses greater than 4 mL should be divided equally into 2 syringes. The product may be held at room temperature for up to 1 hour, but must be administered within 1 hour after reconstitution.

Preparation for Delayed Subcutaneous Administration: The reconstituted product may be kept in the vial or drawn into a syringe. Doses greater than 4 mL should be divided equally into 2 syringes. The product must be refrigerated immediately. When AZACITIDINE is reconstituted using water for injection that has not been refrigerated, the reconstituted product may be held under refrigerated conditions (2ºC - 8ºC, 36ºF - 46ºF) for up to 8 hours. When AZACITIDINE is reconstituted using refrigerated (2ºC - 8ºC, 36ºF - 46ºF) water for injection, the reconstituted product may be stored under refrigerated conditions (2ºC - 8ºC, 36ºF - 46ºF) for up to 22 hours. After removal from refrigerated conditions, the suspension may be allowed to equilibrate to room temperature for up to 30 minutes prior to administration.

Subcutaneous Administration

To provide a homogeneous suspension, the contents of the dosing syringe must be re-suspended immediately prior to administration. To re-suspend, vigorously roll the syringe between the palms until a uniform, cloudy suspension is achieved.

AZACITIDINE suspension is administered subcutaneously. Doses greater than 4 mL should be divided equally into 2 syringes and injected into 2 separate sites. Rotate sites for each injection (thigh, abdomen, or upper arm). New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, red, or hard.

Suspension Stability: AZACITIDINE reconstituted with non-refrigerated water for injection for subcutaneous administration may be stored for up to 1 hour at 25°C (77°F) or for up to 8 hours between 2°C and 8°C (36°F and 46°F); when reconstituted with refrigerated (2ºC - 8ºC, 36ºF - 46ºF) water for injection, it may be stored for 22 hours between 2°C and 8°C (36°F and 46°F).

Instructions for Intravenous Administration

Reconstitute the appropriate number of AZACITIDINE vials to achieve the desired dose. Reconstitute each vial with 10 mL sterile water for injection. Vigorously shake or roll the vial until all solids are dissolved. The resulting solution will contain azacitidine 10 mg/mL. The solution should be clear. Parenteral drug product should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Withdraw the required amount of AZACITIDINE solution to deliver the desired dose and inject into a 50 -100 mL infusion bag of either 0.9% Sodium Chloride Injection or Lactated Ringer's Injection.

Intravenous Administration

AZACITIDINE solution is administered intravenously. Administer the total dose over a period of 10 - 40 minutes. The administration must be completed within 1 hour of reconstitution of the AZACITIDINE vial.

Solution Stability: AZACITIDINE reconstituted for intravenous administration may be stored at 25°C (77°F), but administration must be completed within 1 hour of reconstitution.

Intravenous Solution Incompatibility

AZACITIDINE is incompatible with 5% Dextrose solutions, Hespan, or solutions that contain bicarbonate. These solutions have the potential to increase the rate of degradation of AZACITIDINE and should therefore be avoided.

CONTRAINDICATION

· Azacitidine is contraindicated in patients with advanced malignant hepatic tumors.

· Azacitidine is contraindicated in patients with a known hypersensitivity to azacitidine or mannitol.

PRECAUTIONS AND WARNING

Anemia, Neutropenia and Thrombocytopenia

AZACITIDINE causes anemia, neutropenia and thrombocytopenia. Monitor complete blood counts frequently for response and/or toxicity, at a minimum, prior to each dosing cycle. After administration of the recommended dosage for the first cycle, adjust dosage for subsequent cycles based on nadir counts and hematologic response.

Hepatotoxicity in Patients with Severe Pre-existing Hepatic Impairment

Because azacitidine is potentially hepatotoxic in patients with severe pre-existing hepatic impairment, caution is needed in patients with liver disease. Patients with extensive tumor burden due to metastatic disease have been reported to experience progressive hepatic coma and death during azacitidine treatment, especially in such patients with baseline albumin <30 g/L. Azacitidine is contraindicated in patients with advanced malignant hepatic tumors Monitor liver chemistries prior to initiation of therapy and with each cycle.

Renal Toxicity

Renal toxicity ranging from elevated serum creatinine to renal failure and death have been reported in patients treated with intravenous azacitidine in combination with other chemotherapeutic agents for non MDS conditions. In addition, renal tubular acidosis, defined as a fall in serum bicarbonate to <20 mEq/L in association with an alkaline urine and hypokalemia (serum potassium <3 mEq/L) developed in 5 patients with CML treated with azacitidine and etoposide. Monitor serum creatinine and electrolytes prior to initiation of therapy and with each cycle. If unexplained reductions in serum bicarbonate <20 mEq/L or elevations of BUN or serum creatinine occur, reduce or hold the dose.

Patients with renal impairment may be at increased risk for renal toxicity. Also, azacitidine and its metabolites are primarily excreted by the kidney. Therefore, monitor these patients closely for toxicity.

Tumor Lysis Syndrome

AZACITIDINE may cause fatal or serious tumor lysis syndrome, including in patients with MDS.

Tumor lysis syndrome may occur despite concomitant use of allopurinol. Assess baseline risk and monitor and treat as appropriate.

Embryo-Fetal Risk

Based on the mechanism of action and findings in animals, AZACITIDINE can cause fetal harm when administered to a pregnant woman. Azacitidine administered to pregnant rats via a single intraperitoneal (IP) dose approximating 8% of the recommended human daily dose caused fetal death and anomalies. Advise females with reproductive potential to avoid pregnancy during treatment with AZACITIDINE. Men should be advised to not father a child while receiving treatment with AZACITIDINE.

DRUG INTERACTION

No formal clinical drug interaction studies with azacitidine have been conducted

USE IN SPECIFIC POPULATION

Pregnancy

Based on its mechanism of action and findings in animals, AZACITIDINE can cause fetal harm when administered to a pregnant woman. There are no

data on the use of azacitidine in pregnant women. Azacitidine was teratogenic and caused embryo-fetal lethality in animals at doses lower than the recommended human daily dose. Advise pregnant women of the potential risk to the fetus.

Lactation

There is no information regarding the presence of azacitidine in human milk, the effects of AZACITIDINE on the breastfed infant, or the effects of AZACITIDINE on milk production. Because many drugs are excreted in human milk and because of the potential for tumorigenicity shown for azacitidine in animal studies and the potential for serious adverse reactions in nursing infants from AZACITIDINE, advise patients not to breastfeed during treatment with AZACITIDINE.

Females and Males of Reproductive Potential

Based on its mechanism of action and findings in animals, AZACITIDINE can cause fetal harm when administered to a pregnant woman. Verify the pregnancy status of females of reproductive potential prior to initiating AZACITIDINE.

Female: Advise females of reproductive potential to avoid pregnancy during treatment with AZACITIDINE.

Males: Males with female sexual partners of reproductive potential should not father a child and should use effective contraception during treatment with AZACITIDINE.

Infertility: Based on animal data, azacitidine could have an effect on male or female fertility.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the total number of patients in Studies 1, 2 and 3, 62% were 65 years and older and 21% were 75 years and older. No overall differences in effectiveness were observed between these patients and younger patients. In addition there were no relevant differences in the frequency of adverse reactions observed in patients 65 years and older compared to younger patients.

Of the 179 patients randomized to azacitidine in Study 4, 68% were 65 years and older and 21% were 75 years and older. Survival data for patients 65 years and older were consistent with overall survival results. The majority of adverse reactions occurred at similar frequencies in patients <65 years of age and patients 65 years of age and older.

Elderly patients are more likely to have decreased renal function. Monitor renal function in these patients.

Renal Impairment

Severe renal impairment (creatinine clearance [CLcr] <30 mL/min) has no major effect on the exposure of azacitidine after multiple SC administrations. Therefore, azacitidine can be administered to patients with renal impairment without Cycle 1 dose adjustment.

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			
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		