

Method of administration

Reconstituted Azacitidine 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.

Contraindications

Hypersensitivity to the active substance or to any of the excipients. Breast-feeding. Advanced malignant hepatic tumours.

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.

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. 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.

Special warnings and precautions for use

Warnings and precautions

Blood Test

You will have blood tests before you begin treatment with Azacitidine 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.

Precautions

People with decreased counts of platelets, red or white blood cells, with kidney disease, with had a heart condition or heart attack or any history of lung disease.

Children and adolescents

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

Other medicines and Azacitidine

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

Pregnancy, breast-feeding and fertility

Pregnancy

You should not use Azacitidine 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 or breast-feeding, 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 Azacitidine. It is not known if this medicine passes into human milk.

Fertility

Men should not father a child while receiving treatment with Azacitidine. 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.

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

Overdose

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

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

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.

Pharmaceutical particulars

List of excipients
Mannitol

Special precautions for storage

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

After reconstitution:

Instructions for Intravenous Administration

Azacitidine for Injection should be reconstituted aseptically with 10 mL sterile water for injection. The diluent should be injected slowly into the vial. Vigorously shake or roll the vial until all solids are dissolved. The solution should be clear. The resulting solution will contain Azacitidine 10 mg/mL. Azacitidine reconstituted for intravenous administration may be stored at 25°C (77°F), but administration must be completed within 1 hour of reconstitution.

Instructions for Subcutaneous Administration

Azacitidine for Injection 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 Azacitidine 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.

DESCRIPTION

White Lyophilized powder in 30mL/20mm flint moulded USP type-1 glass vial with 20mm dark grey chloro butyl flurotec coated single slotted rubber stopper and 20mm aluminum flip off seal.

INDICATION

Azacitidine 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,
- AML with >30% marrow blasts according to the WHO classification.

Pharmacotherapeutic group: Antineoplastic agents, antimetabolites, pyrimidine analogues, ATC code: L01BC07

Pharmacology

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.

Pharmacokinetics

Absorption

Following subcutaneous administration of a single 75 mg/m² 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/m² doses) was approximately 89% based on area under the curve (AUC). Area under the curve and maximum plasma concentration (C_{max}) of subcutaneous administration of azacitidine were approximately proportional within the 25 to 100 mg/m² 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 product 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_{1/2}) after subcutaneous administration of 41 ± 8 minutes. No accumulation occurs after subcutaneous administration of 75 mg/m² 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 14C-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/m² 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.

Posology and method of administration

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

Posology

The recommended starting dose for the first treatment cycle, for all patients regardless of baseline haematology laboratory values, is 75 mg/m² of body surface area, injected subcutaneously, daily for 7 days, followed by a rest period of 21 days (28-day treatment cycle).

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

Patients should be monitored for haematologic response/toxicity and renal toxicities 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.

Special populations

Elderly patients

No specific dose adjustments are recommended for the elderly. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function.

Patients with renal impairment

Azacitidine can be administered to patients with renal impairment without initial dose adjustment (see section 5.2). If unexplained reductions in serum bicarbonate levels to less than 20 mmol/L occur, the dose should be reduced by 50 % on the next cycle. If unexplained 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.

Patients with hepatic impairment

No formal studies have been conducted in patients with hepatic impairment. 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. Azacitidine is contraindicated in patients with advanced malignant hepatic tumours.

Paediatric population

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

The shelf life of the reconstituted medicinal product can be extended by reconstituting with refrigerated (2°C to 8°C) water for injections. When Azacitidine 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.

After removal from refrigerated conditions, the suspension should be allowed up to 30 minutes prior to administration to reach a temperature.

Special precautions for disposal and other handling

Recommendations for safe handling

- Azacitidine 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

Azacitidine 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 airtrapped 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.

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7. When more than 1 vial is needed all the above steps for preparation of the suspension

8. should be repeated. For doses requiring more than 1 vial, the dose should be equally divided

e.g., dose 150 mg = 6 mL, 2 syringes with 3 mL in each syringe. Due to retention in the vial and needle, it may not be feasible to withdraw all of the suspension from the vial.

8. The contents of the dosing syringe must be re-suspended immediately prior to administration. The syringe filled with reconstituted suspension should be allowed up to 30 minutes prior to administration to reach a temperature of approximately 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.

9. Storage of the reconstituted product

10. For storage conditions after reconstitution of the medicinal product.

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/m2) x BSA (m2)

The following table is provided only as an example of how to calculate

individual azacitidine doses based on an average BSA value of 1.8 m2.

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

CAUTION: Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without prescription.

KEEP OUT OF REACH OF CHILDREN.

For suspected adverse drug react'on, report to **FDA: www.fda.gov.ph** and email to **pv@biocarelifesciences.com**

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