



MSN LABORATORIES PRIVATE LIMITED		PACKAGING DEVELOPMENT	
Artwork Information		Specification for Printed Leaflet	
		Test	Specification
Brand Name	Azadual 100	Substrate	Bible paper
Generic Name	Azacitidine Powder for Suspension for Injection 100 mg/vial	GSM	40 ± 5% GSM
Open Dimension	260 x 460 ± 2 mm	Mode of supply	Tray pack with suitable quantity
Folding Dimension	30 x 60 ± 2 mm	* Pharma Code	Fornt side: 1895 / Back side: 1896
Folding Type	Booklet type with gluing	Font Type	Times New Roman, OCR-B 10 BT
Item Code	C030583-01	Font Size	7 pt
Supersede Code	C030583-00	Perforation/Non-Perforation	Non-Perforation
Country	Malaysia	Developed by	M. Radhakrishna
Customer	Mega Lifesciences	Reviewed by	K. Harish
Version	01	Colours	Black Outlines not to be print
Date & Time	12.12.2024 & 15:15		
Note: Pharma code & Product name position and direction is not fixed and may vary based on the printer's requirement/ Machine suitability.			

460 mm

260 mm

60 mm

Vascular disorders		hypotension*, hypertension, orthostatic hypotension, haematoma			
Respiratory, thoracic and mediastinal disorders	dyspnoea, epistaxis	Pleural effusion, dyspnoea exertional, pharyngolaryngeal pain		Interstitial lung disease	
Gastrointestinal disorders	Diarrhoea, vomiting, constipation, nausea, abdominal pain (includes upper and abdominal discomfort)	Gastrointestinal haemorrhage* (includes mouth haemorrhage), haemorrhoidal haemorrhage, stomatitis, gingival bleeding, dyspepsia			
Hepatobiliary disorders			hepatic failure*, progressive hepatic coma		
Skin and subcutaneous tissue disorders	petechiae, pruritus (includes generalized), rash, ecchymosis	purpura, alopecia, urticaria, erythema, rash macular	acute febrile neutrophilic dermatosis, pyoderma gangrenosum		Cutaneous vasculitis
Musculoskeletal, and connective tissue disorders	arthralgia, musculoskeletal pain (includes back, bone and pain in extremity)	muscle spasms, myalgia			
Renal and urinary disorders		renal failure*, haematuria, elevated serum creatinine	renal tubular acidosis		
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

Hematologic 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 study. The majority of adverse reactions occurred during the first 2 cycles of treatment and tended to decrease with subsequent cycles. Subcutaneous adverse reactions such as injection site rash/inflammation/pruritus, rash, erythema and skin lesion may require management with concomitant medicinal products, such as antihistamines, corticosteroids and non-steroidal anti-inflammatory medicinal products (NSAIDs). These cutaneous reactions have to be distinguished from soft tissue infections, sometimes occurring at injection site. Soft tissue infections, including cellulitis and necrotising fasciitis in rare cases leading to death, have been reported with azacitidine in the post marketing setting. For clinical management of infectious adverse reactions.

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 study allowing enrolment of patients with known history of cardiovascular or pulmonary disease showed an increase in cardiac events in patients with newly diagnosed AML treated with azacitidine.

Overdose

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.

Pharmacological properties

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 cancersuppressing functions to cancer cells. The relative importance of DNA hypomethylation versus cytotoxicity or other activities of azacitidine to clinical outcomes has not been established.

Pharmacokinetic properties

The pharmacokinetics of azacitidine were studied in 6 MDS patients following a single 75 mg/m² subcutaneous dose and a single 75 mg/m² intravenous dose.

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 the under the curve (AUC).

Area under the curve and maximum plasma concentration (C_{max}) of subcutaneous admininstration 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 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 (t½) 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, 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.

Pharmacogenomics

The effect of known cytidine deaminase polymorphisms on azacitidine metabolism has not been formally investigated.

Pharmaceutical particulars

List of excipients:

Mannitol, Acetonitrile, Nitrogen, Water.

Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section special precautions for disposal and other handling.

Special precautions for storage

Unopened vials

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

Reconstituted Medicinal Product:

The drug product was stable when stored in vial and syringe up to 60 minutes at room temperature after reconstitution with non-refrigerator water.

The drug product was stable when stored in vial and syringe up to 24 hours at 2-8°C (Refrigerated) condition after reconstitution with non-refrigerator water.

The drug product was stable when stored in vial up to 36 hours at 2-8°C (Refrigerated) condition after reconstitution with refrigerator water.

The drug product was stable when stored in syringe up to 30 hours at 2-8°C (Refrigerated) condition after reconstitution with refrigerator water.

Nature and contents of container

Type 1, clear glass. 30 mL/20 mm moulded flint glass vial with 20mm igloo designbromobutyl coated single slotted rubber stopper with 20 mm aluminium flip of seals. The glass vial is packed in an outer carton along with package insert.

Pack size: 1 vial

Special precautions for disposal and other handling

Recommendations for safe handling

AZADUAL 100 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

AZADUAL 100 should be reconstituted with water for injections. The shelf life of the reconstituted medicinal product can be extended by reconstituting with refrigerated (2°C to 8°C) water for injections. Details on storage of the reconstituted product are provided below.

1. The following supplies should be assembled:

Vial(s) of azacitidine; vial(s) of water for injections; non-sterile surgical gloves; alcohol wipes; 5 mL injection syringe(s) with needle(s).

2. 4 mL of water for injections should be drawn into the syringe, making sure to purge any air trapped within the syringe.

3. The needle of the syringe containing the 4 mL of water for injections should be inserted through the rubber top of the azacitidine vial followed by injection of the water for injections into the vial.

4. Following removal of the syringe and needle, the vial should be vigorously shaken until a uniform cloudy suspension is achieved. After reconstitution each mL of suspension will contain 25 mg of azacitidine (100 mg/4 mL). The reconstituted product is a homogeneous, cloudy suspension, free of agglomerates. The product should be discarded if it contains large particles or agglomerates. Do not filter the suspension after reconstitution since this could remove the active substance. It must be taken into account that filters are present in some adaptors, spikes and closed systems; therefore such systems should not be used for administration of the drug after reconstitution.

5. The rubber top should be cleaned and a new syringe with needle inserted into the vial. The vial should then be turned upside down, making sure the needle tip is below the level of the liquid. The plunger should then be pulled back to withdraw the amount of medicinal product required for the proper dose, making sure to purge any air trapped within the syringe. The syringe with needle should then be removed from the vial and the needle disposed of.

6. A fresh subcutaneous needle (recommended 25-gauge) should then be firmly attached to the syringe. The needle should not be purged prior to injection, in order to reduce the incidence of local injection site reactions.

7. When more than 1 vial is needed all the above steps for preparation of the suspension should be repeated. For doses requiring more than 1 vial, the dose should be equally divided e.g., dose 150 mg = 6 mL, 2 syringes with 3 mL in each syringe. Due to retention in the vial and needle, it may not be feasible to withdraw all of the suspension from the vial.

8. The contents of the dosing syringe must be re-suspended immediately prior to administration.

The syringe filled with reconstituted suspension should be allowed up to 30 minutes prior to administration to reach a temperature of approximately 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.

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

Controlled Medicine/ Ubat Terkawal
Jauhi ubat dari kanak-kanak.

Product Registration Holder:
MEGA LIFESCIENCES SDN BHD
B-28-02, The Ascent, Paradigm.
No.1, Jalan SS7/26A, Kelana Jaya,
47301 Petaling Jaya,Selangor, Malaysia.

Manufactured by:
MSN Laboratories Private Limited,
Formulation Division,
Unit-II, Sy.No. 1277,1319 to 1324,
Nandigama (Village & Mandal),
Rangareddy (District),
Telangana - 509 228, India.

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