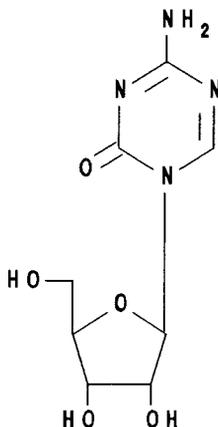


AZACITIDINE

NSC - 102816



Chemical Name: 4-Amino-1-β-D-ribofuranosyl-1,3,5-triazin-2(1H)-one

Other Names: 5-Azacitidine, Ladakamycin, Mylosar[®], Azacitidine (USAN)

CAS Registry Number: 320-67-2

Molecular Formula: $C_8H_{12}N_4O_5$

M.W.: 244.2

How Supplied: For injection, 100 mg, vial: supplied as a white lyophilized powder with 100 mg of mannitol, USP, in 30 mL flint vials.

Solution Preparation: 100 mg/vial : When constituted with 19.9 mL of Sterile Water for Injection, USP, each milliliter contains 5 mg of azacitidine and 5 mg of mannitol, USP. The pH of the resulting solution is 6.0 to 7.5.

The constituted solution can be further diluted in Lactated Ringer's Injection, USP. The pH of this solution, at a concentration of 100 mg/500 mL, is approximately 6.4. Lactated Ringer's Injection, USP, provides optimum pH for solution stability.

Storage: Store the intact vials at refrigeration temperature (2-8 °C).

Stability: The intact vials are stable for at least 4 years at refrigeration temperature (2-8 °C). Room temperature storage (22-25 °C) has not altered the chemical potency of the product after 3 years, but because of degradation at elevated temperatures, refrigeration storage is recommended when possible.

The constituted solutions hydrolyze at room temperature and should be used within 30 minutes for delivery of maximum potency.

The mode of decomposition in the neutral pH range involves opening the triazine ring. Hydration of the 5,6-imine double bond occurs, followed by bond cleavage to yield the formyl derivative, N-(formylamidino)-N- β -D-ribofuranosylurea. Evaluations of the kinetics and mechanism of degradation of azacitidine have been reported in the literature (1,2,3,4). The pH providing optimum stability has been shown to be 6.5 to 7 (1,2,4).

Constitution as recommended with Sterile Water for Injection, USP, provides a solution with a pH value near the optimal pH. Nevertheless, the decomposition rate is rapid, and the time to 10% decomposition is very brief. The constituted solution should be used immediately or further diluted in an appropriate infusion solution and used within 30 minutes.

The stability of azacitidine 0.2 mg/mL and 2 mg/mL in several intravenous infusion solutions has been studied (5). Using a stability-indicating HPLC assay technique, azacitidine stability was found to depend, to a degree, on drug concentration and the specific infusion solution used. However, in all cases the time to 10% decomposition at 25 °C was found to be short. The results of the study are summarized in the following table:

**Stability of Azacitidine in
Various Infusion Fluids at 25 °C**

Infusion Solution	Azacitidine Concentration (mg/mL)	Time to 10% Decomn. (hr)	Concentration after 6 hours (%)
<u>NS</u>			
PVC	0.2	1.6	77
Glass	0.2	1.9	79
Glass	2	2.4	82
<u>D5W</u>			
PVC	0.2	0.7	63
Glass	0.2	0.8	74
<u>LR</u>			
PVC	0.2	2.0	80
Glass	0.2	1.9	79
Glass	2	2.9	82
<u>NR</u>			
Glass	0.2	1.9	76
Glass	2	3.0	84

NS = 0.9% Sodium Chloride Injection, USP
D5W = 5% Dextrose Injection, USP
LR = Lactated Ringer's Injection, USP
NR = Normosol - R (pH 7.4)
PVC = Polyvinyl chloride bags

Route of Administration: Intravenous, subcutaneous

References:

1. Pithova P, Piskala J, Pitha J and Sorm F: Nucleic acid components and their analogues. LXVI. Hydrolysis of 5-azacytidine and its connection with biological activity, Coll Czech Chem Commun 30:2801-2811, 1965.
2. Notari RE and DeYoung JL: Kinetics and mechanisms of degradation of the anti-leukemic agent 5-azacytidine in aqueous solutions, J Pharm Sci 64:1148-1156, 1975.
3. Beisler JA: Isolation, characterization and properties of a labile hydrolysis product of the antitumor nucleoside 5-Azacytidine, J Med Chem 21:204-208, 1978.
4. Chan KK, et al.: 5-Azacytidine hydrolysis kinetics measured by high-pressure liquid chromatography and ^{13}C - NMR spectroscopy, J Pharm Sci 68:807-812, 1979.
5. Cheung YW, Vishnuvajjala BR, Morris NL, Flora, KP, and Craddock, JC: Stability of Azacytidine in infusion fluids, Am J Hosp Pharm 41:1156-1159, 1984.