Stability Of Azacitidine Solutions In Sterile Water For Injection

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INTRODUCTION

Azacitidine is currently indicated for the treatment of intermediate-2 & high-risk Myelodysplastic Syndrome (MDS) and Acute Myeloid Leukemia (AML) with 20-30% blasts with multi lineage dysplasia for patients unable to tolerate high dose chemotherapy.

The original VIDAZA® product monograph indicated that following reconstitution the product must be refrigerated immediately, and may be held under refrigerated conditions (2°C - 8°C) for up to 8 hours. After removal from refrigerated conditions, the suspension may be allowed to equilibrate to room temperature for up to 30 minutes prior to administration.

A 2012 CJHP publication identified that reconstitution with cold sterile water for injection (SWFI) is an important step in extending the before use date.

Extending the before use date would reduce wastage of many drugs. NAPRA guidelines state that the Beyond Use Date must not exceed the earliest of the dates established by the following two criteria:
- Expiration date based on chemical and physical stability according to reference texts
- Storage time related to risk of microbial contamination

The introduction of a generic version of azacitidine (Dr.Reddy’s) in 2017 raised questions of the stability of the generic formulation and the validity of extending stability from one brand to another.

OBJECTIVES

The objective of this study was to evaluate the stability of reconstituted 25 mg/mL and 10 mg/mL azacitidine in the original manufacturer’s vial and in 5mL polypropylene syringes at -20°C, 4°C and 25°C.

METHODS

Liquid Chromatographic Method & Validation

The liquid chromatographic system, consisting of a Waters Nova Pak column and a potassium phosphate mobile phase run at 1 ml/min with UV detection, separated azacitidine from degradation products.

Assay Validation

The absolute deviation from the known concentration from quality control samples on any day averaged 2.1%. The error of replicate analysis within a day averaged less than 0.29% for the standards. Inter-day variation, as measured by the observed standard deviation of regression (Sy.x) for percent remaining, averaged 0.88% across all temperature, concentration and container combinations.

RESULTS

Stability Study: Vials at 25°C.

On study day 0, 6 vials were reconstituted with SWFI as per manufacturer’s instruction and 6 were prepared with COLD (4°C) SWFI to prepare concentrations of 10 mg/mL and 25 mg/mL. All vials were stored at room temperature (25°C). Immediately following reconstitution and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 and 24hr the concentration of azacitidine was determined.

Stability Study: Vials and Syringes at 4°C.

On study day 0, 8 vials were reconstituted with COLD (4°C) SWFI to prepare vials and syringes with concentrations of 10 mg/mL and 25 mg/mL. All vials and syringes were refrigerated (4°C) and sampled at 8, 24, 32, 72 and 96hr. The concentration of azacitidine was determined in duplicate.

Stability Study: Vials and Syringes at -20°C.

On study day 0, 8 vials were reconstituted with COLD (4°C) SWFI to prepare vials and syringes with concentrations of 10 mg/mL and 25 mg/mL. All vials and syringes were stored in the freezer at -20°C. Immediately following reconstitution and on days 1, 3, 7, 10, 14, 17 and 21 the azacitidine concentration was determined in duplicate.

Data Reduction and Statistical Analysis

Analysis of variance was used to test differences in degradation rate between various temperature–diluent–concentration combinations. The 5% level was used as the a priori cut-off for significance. The concentration of a solution on a particular day was considered “acceptable” or “within acceptable limits” if it was greater than 90% of the initial concentration (as determined on day 0) and the amount found on that day, with 95% confidence.

CONCLUSION

There appears to be no difference in the stability of the Dr.Reddy’s and Celgene formulations. Reconstitution with cold SWFI is an important step in extending the before use date. We recommend that immediately following reconstitution with cold SWFI, vials and syringes be stored at 4°C. The maximum period of storage at 4°C is 8 hours. If a vial is unused after 8 hours or at the end of the day, we recommend the vial be placed in the freezer at -20°C. The maximum period of storage at -20°C is 4 days. At any time prior to the 4th day the vial can be removed from the freezer, thawed, syringes prepared and the solution administered to patients. If the time between removal from the freezer and administration to the patient does not exceed 2 hours (30 minutes to thaw and 1.5 hours to allow delivery and administration to the patient) more than 90% of the initial concentration will remain with 95% confidence.

If these storage conditions / limitations are used, wastage can be reduced (possibly eliminated) providing significant cost savings.