Stability of a New Generic Formulation of Bortezomib Injection (Apotex brand) In Vials and Syringes Stored at 4°C and Room Temperature (25°C)

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INTRODUCTION

Bortezomib is the backbone of various treatment regimens used to treat multiple myeloma both in the first line setting (stem cell transplant and non stem cell transplant candidates) and in the relapsed/refractory setting. It is available in Canada as 3.5 mg of sterile lyophilized powder in a 10-mL clear glass vial, intended for reconstitution with 0.9% sodium chloride (NS).

A 2008 CJHP publication[1] demonstrated that 1.0 mg/mL solutions of bortezomib (Velcade®) retained more than 95% of the initial concentration for up to 42 days when stored at either 4°C or 25°C.

Bortezomib was typically administered IV; however, a May 2011 report in Lancet Oncology[2] demonstrated that subcutaneous bortezomib has an improved safety profile and similar efficacy compared to IV administration in 222 myeloma patients in the relapse setting.

A 2014 CJHP publication[3] demonstrated that 2.5 mg/mL solutions of bortezomib retained more than 95% of the initial concentration for up to 21 days when stored at either 4°C or 25°C.

The introduction of a generic version of bortezomib (Apotex) in 2019 raised questions of the stability of the generic formulation and the validity of extending stability from one brand to another.

OBJECTIVES

It was the objective of this study to evaluate the stability of bortezomib 1.0 and 2.5 mg/mL solutions stored in the original manufacturer's vial or Equashield® syringes following reconstitution of the 3.5 mg vial with 0.9% NS over 42 days when stored at either 4°C or 25°C.

The concentration of bortezomib in vials and syringes was evaluated during storage at each temperature using a validated, stability indicating, liquid chromatographic method using UV detection.

1: Walker SE, *et al.* Can J Hosp Pharm. 2008;61(1):14-20.
2: Moreau P, *et al.* Lancet Oncol. 2011;12(5):431-40.
3: Walker SE, *et al.* Can J Hosp Pharm. 2014;67(2):102-7.

NONE of the authors of this poster have any personal or financial relationships with any commercial entities that may have a direct or indirect interest in the subject matter of this presentation.
The bortezomib used in this study was donated by Apotex Inc .

METHODS

Liquid Chromatographic Method

The liquid chromatographic system consisted of a mixture of 15% methanol and 85% 0.04 mol/L potassium phosphate monobasic buffer (pH of 7) which was pumped through 15 cm x 4.6 mm reverse-phase C18, 3-µm column (Supelcosil; Supelco, Toronto, Ontario) at 1.0 mL/min.

Assay Validation

The previously published method was re-evaluated to ensure reproducibility, accuracy and assay specificity. The system was shown to be capable of separating bortezomib from its degradation products (Figure 1). Accuracy and reproducibility of standard curves was tested over 5 days. Inter- and intra-day errors of reproducibility were assessed by the coefficients of variation and the standard deviation of regression.

Stability Study: Vials and Syringes at 4°C and 25°C

On study day 0, 24 x 3.5 mg vials of bortezomib (Apotex Inc.; Lot: BORAC1048, Expiry: 11-20) were each reconstituted with NS. The contents of 9 vials were each reconstituted with 3.5 mL of NS to prepare 1 mg/mL solutions in 6 manufacturer's vials and 6 x 3mL Equashield® syringes containing 1.75 mL. The contents of an additional 12 vials were each reconstituted with 1.4 mL of NS to prepare 2.5 mg/mL solutions in 6 manufacturer's vials and 6 x 3mL Equashield® syringes containing 1.4 mL. Three of each container (vials and Equashield® syringes) were stored at room temperature and 3 were stored in the refrigerator. Concentration and physical inspection were completed on study days 0, 1, 2, 4, 8, 11, 15, 18, 21, 28, 35 and 42. The bortezomib concentration was determined by the validated liquid chromatographic method with UV detection at 270 nm.

Data Reduction and Statistical Analysis

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, was also greater than 90% of the initial concentration. Analysis of variance was used to test differences in degradation rate between the different storage temperatures and container combinations. The 5% level was used as the *a priori* cut-off for significance.

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CONCLUSIONS

We conclude that 3.5-mg Apotex vials of bortezomib reconstituted with 1.4 mL of NS to create a 2.5 mg/mL solution or 3.5 mL of NS to create a 1.0 mg/mL solution are physically and chemically stable for at least 42 days at 4°C or 25°C in both Equashield® syringes and the original manufacturer's glass vial.

The generic version of Apotex bortezomib is reported to be pharmaceutically similar to Velcade® and this study demonstrates that the chemical stability of the Apotex formulation is similar to the stability of the Velcade® formulation previously reported. When establishing a beyond use date (BUD), both the stability of the components and the sterility limits established by NAPRA/USP 797 must be considered.

RESULTS

Table 1. Percent Remaining of the Initial Bortezomib Concentration[1].

	Vial[2] 4°C	Syringe[3] 4°C	Vial[2] 25°C	Syringe[3] 25°C	Vial[2] 4°C	Syringe[3] 4°C	Vial[2] 25°C	Syringe[3] 25°C
Nominal Initial concentration (mg/mL)	1mg/mL	1mg/mL	1mg/mL	1mg/mL	2.5mg/mL	2.5mg/mL	2.5mg/mL	2.5mg/mL
Study Day / Initial concentration (mg/mL)	1.04±0.16	1.05±0.59	1.05±0.53	1.05±0.36	2.46±0.35	2.48±0.13	2.45±0.16	2.47±0.31
1	99.61±0.76	98.64±0.80	98.54±0.23	98.88±0.30	100.40±0.57	99.82±0.69	100.61±0.65	100.20±0.16
4	99.64±0.23	98.73±0.67	99.38±0.32	99.14±0.56	100.14±1.04	99.49±1.03	100.45±0.34	99.15±0.48
8	101.63±0.40	100.84±0.63	99.94±0.72	100.35±0.77	103.42±0.69	103.29±0.36	99.88±0.37	100.01±1.04
11	99.51±0.32	99.37±0.57	99.76±0.33	99.21±0.78	103.55±1.11	102.38±0.02	99.80±1.33	98.01±0.30
15	99.51±0.06	98.18±1.44	98.21±0.25	98.19±0.53	97.54±0.56	97.17±0.44	97.23±1.83	97.20±0.67
18	99.53±0.38	100.78±0.21	98.27±0.48	98.74±0.32	102.86±1.10	102.25±0.11	98.59±0.66	97.55±0.69
21	101.12±0.18	100.27±0.91	98.72±2.57	97.16±0.26	101.44±0.60	100.67±0.35	97.25±0.14	97.36±0.47
28	98.05±0.22	97.75±0.67	97.87±0.98	96.19±0.80	99.18±0.28	98.57±0.46	96.64±0.16	96.27±0.36
35	99.28±0.06	98.53±0.60	96.31±0.54	96.01±0.46	99.12±0.15	98.52±0.69	95.21±0.34	96.41±3.61
42	99.75±0.05	98.15±0.28	95.23±0.51	95.04±0.40	98.72±0.35	98.20±0.14	94.95±0.12	95.10±0.31
Degradation Rate (%/day) [Slope]	-0.019	-0.032	-0.096	-0.117	-0.053	-0.058	-0.144	-0.117
Standard Deviation of Regression (Sy.x)	0.944	1.069	0.723	0.684	1.967	1.867	0.628	0.594
Shortest T-90 in days (95% CI)	146.75	115.26	74.77	65.85	64.85	64.87	56.70	67.93

1. Concentrations are shown as ± the Coefficient of Variation (CV), expressed as a percentage
2. Manufacturer's (Apotex) original glass vial with EquaShield Closed System Transfer Device applied.
3. Syringe is an EquaShield Closed System Transfer Syringe.

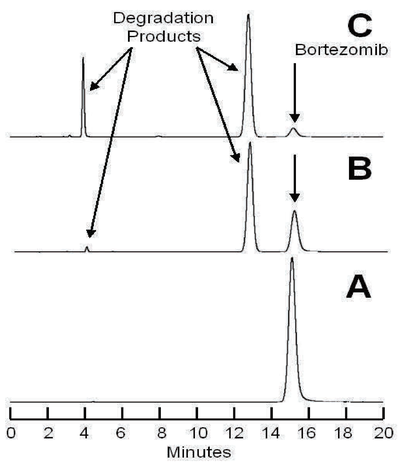

Figure 1.
Chromatogram A represents a solution of 1.0 mg/mL bortezomib in water prior to the addition on sodium hypochlorite. Chromatogram B was chromatographed immediately after the addition of 5uL of 0.3% sodium hypochlorite. 29% of the initial bortezomib was observed to remain. Chromatogram C was chromatographed immediately after the addition of 5uL of 0.4% sodium hypochlorite. 12% of the initial bortezomib was observed to remain. Degradation products appear at 3.7 and 13.5 minutes. Additional products appeared at 4.3, 4.8, 8.7 and 29 minutes.

Assay Validation

Assay validation demonstrated that degradation products are separated from bortezomib (Figure 1). Standards and quality control samples over the study period showed an average absolute deviation of 2.1% from the expected concentration. Analytical error with replicate measurement (as measured by coefficient of variation) averaged 0.44% within a day, 2.19% between days and the standard deviation of regression averaged 1.06%.

Concentration Results

Concentrations on each study day are reported in Table 1. During the study period all solutions retained more than 95% of the initial concentration in vials and syringes at both temperatures and concentrations. The calculated use-before-date, with 95% confidence, exceeded 42 days for all temperatures, concentrations and container combinations.

Analysis of variance revealed significant differences in percent remaining due to study day ($p < 0.001$) and temperature ($p < 0.001$), but not container ($p = 0.112$) or concentration ($p = 0.223$). This study was capable of detecting a 0.89% difference in concentration due to study day, temperature, concentration or container. The average difference due to temperature translates into a difference of ~ 2% on day 42.