STABILITY OF 1.0 AND 2.5 MG/ML BORTEZOMIB IN VIALS AND SYRINGES FOLLOWING RECONSTITUTION WITH SODIUM CHLORIDE AT 40°C AND 230°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 CHIP publication 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.

However, a May 2011 report in Lancet Oncology 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 CHIP publication demonstrated that 2.5 mg/ml solutions of bortezomib (Velcade®) 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 (Dr.Reddy’s) in 2016 raised questions of the stability of the generic formulation and the validity of extending stability from one brand to another.

OBJECTIVE:
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 syringes following reconstitution of the 3.5 mg vial with 0.9% sodium chloride (NS) over 21 days.

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.

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 (Supelcoil; 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 3.5mg vials of bortezomib (Dr.Reddy’s; Lot: H7005, Expiry: 06 - 2018) were each reconstituted with sodium chloride. 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 3 mL Equashield® syringes containing 1.75 mL. The contents of a further 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 3 mL Equashield® syringes containing 1.4 mL. 3 of each container (vials and 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, 3, 7, 11, 14, and 21. 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 cutoff for significance.

RESULTS:

Table 1. Percent Remaining of the Initial Bortezomib Concentration

<table>
<thead>
<tr>
<th>Container Type</th>
<th>Concentration</th>
<th>Initial concentration</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 7</th>
<th>Day 11</th>
<th>Day 14</th>
<th>Day 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vial</td>
<td>1.0 mg/ml</td>
<td>100%</td>
<td>95%</td>
<td>95%</td>
<td>95%</td>
<td>95%</td>
<td>95%</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>Syringe</td>
<td>1.0 mg/ml</td>
<td>100%</td>
<td>95%</td>
<td>95%</td>
<td>95%</td>
<td>95%</td>
<td>95%</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>Vial</td>
<td>2.5 mg/ml</td>
<td>100%</td>
<td>95%</td>
<td>95%</td>
<td>95%</td>
<td>95%</td>
<td>95%</td>
<td>95%</td>
<td>95%</td>
</tr>
<tr>
<td>Syringe</td>
<td>2.5 mg/ml</td>
<td>100%</td>
<td>95%</td>
<td>95%</td>
<td>95%</td>
<td>95%</td>
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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 5% sodium hypochlorite. 29% of the initial bortezomib was observed to remain. Chromatogram C was chromatographed immediately after the addition of 5% sodium hypochlorite. 12% of the initial bortezomib was observed to remain. Degradation products appear at 3.7 and 13.5 minutes. Additional products appear at 6.8, 6.7 and 59 minutes.

CONCLUSION:
We conclude that 3.5-mg Dr. Reddy’s 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 21 days at 4°C or room temperature in both Equashield syringes and the original manufacturer’s glass vial.

Dr.Reddy’s generic version of bortezomib is reported to be pharmaceutically similar to VELCADE® and this study demonstrates that the chemical stability of the Dr.Reddy’s formulation is similar to the stability of the VELCADE® formulation previously reported.