Stability of Generic Formulations of Bortezomib 1.0 and 2.5 mg/mL in Vials and Syringes Stored 4°C and Room Temperature (23°C)

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INTRODUCTION

Differences in published reports on the stability of various parenteral drugs considered pharmaceutically equivalent and an interpretation of the recent National Association of Retailer Pharmacy-Regulatory Authorities (NAPRA) guidelines, has led some to conclude that each institution should conduct separate evaluations of the stability of each formulation used in their institution.

METHODS

To evaluate the stability of Janssen, Teva, Actavis and Dr.Reddy’s bortezomib formulations reconstituted to produce either 1.0 or 2.5 mg/mL, during storage at least 21 days at room temperature (23°C) and under refrigeration (4°C) in plastic syringes and manufacturer vials.

RESULTS

This study failed to detect differences in bortezomib stability due to manufacturer. Furthermore, the shortest time to achieve 90% of the initial concentration, with 95% confidence (T-90 [95% CI]) exceeds 25 days in all studied containers, at all temperatures, with all manufacturers and concentration objectives in accordance with the FDA HD 2015 guidelines.

CONCLUSION

Two head-to-head stability studies comparing different manufacturer’s brands of vancomycin and a morphinan analog of cefazolin and vancomycin studies also failed to observe differences in stability as the result of manufacturer. Future research on manufacturer differences in stability should focus on drugs with shorter expiry (e.g. antibiotics) or stable drugs where sterility tests are used to extend BUDs.

Table 1. Data summary of the Bortezomib Concentrations in all Four Studies.

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Janssen</th>
<th>Teva</th>
<th>Actavis</th>
<th>Dr. Reddy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>100.00</td>
<td>100.00</td>
<td>100.00</td>
<td>100.00</td>
</tr>
<tr>
<td>18%</td>
<td>95.64</td>
<td>97.90</td>
<td>96.24</td>
<td>96.26</td>
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<td>36%</td>
<td>90.71</td>
<td>92.24</td>
<td>91.79</td>
<td>92.55</td>
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<tr>
<td>54%</td>
<td>85.63</td>
<td>88.14</td>
<td>87.34</td>
<td>88.42</td>
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<tr>
<td>72%</td>
<td>80.32</td>
<td>83.00</td>
<td>82.37</td>
<td>83.62</td>
</tr>
<tr>
<td>90%</td>
<td>75.90</td>
<td>79.40</td>
<td>78.80</td>
<td>79.81</td>
</tr>
<tr>
<td>100%</td>
<td>71.26</td>
<td>74.93</td>
<td>74.34</td>
<td>75.29</td>
</tr>
</tbody>
</table>

4. Stability of bortezomib at an intermediate concentration (0.5 mg/mL) was evaluated using analysis of variance (ANOVA) and regression analysis. The stability results are presented as a percentage of the initial concentration at each storage condition. Statistical significance was set at p<0.05.

To ensure homogeneity within the data set, the standard deviation of regression (which varied from 0.35% to 1.57%); Table 1 was evaluated for differences by ANOVA. ANOVA failed to detect significant differences in the standard deviation of regression due to the factors of manufacturer (p=0.931), temperature (p=0.854), concentration (p=0.241) or container (p=0.833). Furthermore, there was no correlation between the standard deviation of regression and the time to achieve 90% of the initial concentration - with 95% confidence (T-90 [95% CI]) observed in the study (r=0.303, n=30; p=0.706). The results indicate that the standard deviation of regression is, effectively, a random variable in the analysis.

In the evaluation of the T-90 [95% CI], analysis of variance failed to detect significant differences due to manufacturer (p=0.970), temperature (p=0.088), concentration (p=0.681), or container (p=0.465).

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