ARTICLE

Stability of Bortezomib Reconstituted with 0.9% Sodium Chloride at 4°C and Room Temperature (23°C)

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ABSTRACT

Background: The bortezomib product monograph indicates that after reconstitution, the drug may be stored for up to 3 h in a syringe, and the total storage time for the reconstituted material must not exceed 8 h when exposed to normal indoor lighting. Given the product packaging and vial size, as well as the currently recommended dosage regimen (which, for a clinic treating between 1 and 10 patients daily, entails using about half a vial each day), there is potential for substantial wastage, about $13,000 for a 5-cycle course of bortezomib therapy for a single patient. The aim of this study was to evaluate the stability of bortezomib (3.5-mg vials) reconstituted with 3.5 mL of 0.9% sodium chloride (NS) to produce a 1 mg/mL solution.

Methods: On study day 0, six 3.5-mg vials of bortezomib were reconstituted with 3.5 mL NS per vial, to prepare solutions of 1.0 mg/mL. Three of the vials were stored in the refrigerator, and 3 were stored at room temperature. Concentration was measured and physical inspection was completed for each vial on study days 0, 1, 4, 8, 11, 15, 18, 21, 28, 34, and 42. The intervals between study days were consistent with the recommended dosage regimen, as published in the product monograph. Bortezomib concentrations were determined by a validated, stability-indicating, liquid chromatographic method.

Results: All solutions remained clear and colourless. During the study period, all solutions retained more than 98% of the initial concentration, and the amount remaining on day 42 was greater than 98% (with 95% confidence). During the study period, the absolute deviation from the known concentration for standards and quality control samples averaged less than 4%, and analytical reproducibility within a day (by coefficient of variation) was high, with error on replicate analysis averaging less than 2%.

Conclusions: Bortezomib, supplied in 3.5-mg vials and reconstituted with 3.5 mL NS, is physically and chemically stable for up to 42 days at 4°C or at room temperature.

Key words: bortezomib, drug stability

RÉSUMÉ

Historique : La monographie du bortézomib mentionne qu'après reconstitution, le médicament peut être conservé jusqu'à trois heures dans une seringue, mais que la durée totale de conservation du médicament reconstitué ne doit pas dépasser huit heures si le produit est exposé à un éclairage intérieur normal. Vu le conditionnement du produit, le format des fioles et la posologie recommandée actuellement (qui, dans une clinique qui traite de 1 à 10 patients par jour, signifie l'emploi d'environ une demi-fiole par jour), le potentiel de gaspillage est considérable, et peut être évalué à environ 13 000 dollars pour cinq cycles de traitement par le bortézomib pour un seul patient. L'objectif de cette étude était d'évaluer la stabilité du bortézomib (en fioles de 3,5 mg) reconstitué avec 3,5 mL de chlorure de sodium à 0,9 % (NS) pour obtenir une concentration de 1 mg/mL.

Méthodes : Au jour 0, on a reconstitué six fioles de 3,5 mg de bortézomib avec 3,5 mL de NS par fiole, pour obtenir des solutions à 1.0 mg/mL. Trois des fioles ont été entreposées au réfrigérateur et les trois autres, à la température ambiante. La concentration a été mesurée et une inspection physique a été effectuée pour chaque fiole aux jours 0, 1, 4, 8, 11, 15, 18, 21, 28, 34 et 42 de l'étude. Les intervalles entre les jours de l'étude correspondaient à l'intervalle posologique recommandé conformément à la monographie du produit. Les concentrations de bortézomib ont été déterminées au moyen d'une épreuve de stabilité par chromatographie liquide validée.

Résultats : Toutes les solutions sont demeurées limpides et incolores. Pendant la période de l'étude, toutes les solutions ont conservé plus de 98 % de leur concentration initiale, et il en était de même au jour 42 (intervalle de confiance à 95 %). Pendant la période de l'étude, l'écart absolu par rapport à la concentration connue des échantillons de référence et de contrôle de la qualité était en moyenne inférieur à 4 %, et la reproductibilité analytique au cours d'une journée (selon le coefficient de variation) était élevée, avec une erreur moyenne entre les mesures inférieure à 2 %.

Conclusions : Les solutions obtenues à partir de la reconstitution du contenu d'une fiole de 3,5 mg de bortézomib avec 3,5 mL de NS sont physiquement et chimiquement stables pendant une période allant jusqu'à 42 jours à une température de 4 °C ou à la température ambiante.

Mots clés : bortézomib, stabilité des médicaments

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INTRODUCTION

Bortezomib is indicated for the treatment of patients with multiple myeloma who have experienced relapse after first-line therapy.[1] It is available in Canada as 3.5 mg of sterile lyophilized powder in a 10-mL clear glass vial, intended for reconstitution with 3.5 mL of 0.9% sodium chloride (NS) to prepare a 1 mg/mL solution. The bortezomib product monograph indicates that bortezomib reconstituted in this way may be stored for up to 3 h in a syringe, and total storage time for the reconstituted material must not exceed 8 h when exposed to normal indoor lighting. Given the product packaging and vial size, as well as the recommended dose of 1.3 mg/m^2 body surface area, there is potential for considerable wastage, about $13,000 for a 5-cycle course of bortezomib therapy for a single patient. With an expiry time of 8 h, the actual cost of wastage depends on the patient's body surface area and the number of patients appearing at the clinic on a given day. A clinic treating between 1 and 10 patients per day with an average body surface area of 1.7 m^2 per patient could waste half of a 3.5-mg vial each clinic day. Therefore, evaluating the stability of bortezomib was considered an important step in minimizing the cost of bortezomib wastage.[2]

In July 2005, plans for this study began. A literature search at that time did not identify any publications describing the stability of bortezomib or any previously published stability-indicating methods for this drug. Therefore, before initiating the stability study, a stability-indicating analytical method for bortezomib had to be developed and validated.[3-5] Assay development began in August 2005, but shortly thereafter, a relevant article by André and others[6] became available. The stability-indicating nature of the ultraviolet liquid chromatographic method used by those authors is well documented, and since all equipment and materials were readily available, the authors of the current study began to set up and validate the method reported by André and others.[6] The decision to repeat the study was based on 3 factors: first, André and others[6] used solution remaining in a vial after patients' doses had been removed (i.e., waste); second, they stopped their sample analysis after the concentration on any one day dropped below 90%; and third, they did not report 95% confidence intervals (CIs) for the percent remaining on the final study days. Furthermore, analysis of the mean data reported by André and others[6] seemed to show stability over the first 5 days at 5°C, followed by a more rapid decline in concentration between days 8 and 11. On further inspection, deviations between the observed data and the amount estimated to remain by linear regression doubled for day 8 (syringes) and day 11 (vials), which suggested that the expiry date reported by André and others[6] could be extended.

The objective of the study reported here was to evaluate the stability of bortezomib (supplied in 3.5-mg vials, each reconstituted with 3.5 mL of NS to produce a 1 mg/mL solution) during storage at 4°C and at room temperature (23°C) over 42 days.

METHODS

Chromatographic Analysis

The stability-indicating method of André and others[6] was set up in the authors' laboratory. The liquid chromatographic system consisted of a solvent delivery pump (model P4000, Thermo Separation Products, Fremont, California), which pumped a mixture of 50% methanol and 50% 0.04 mol/L potassium phosphate monobasic (high-performance liquid chromatography grade, catalogue no. P286-1, Fisher Scientific, Fair Lawn, New Jersey). The pH of the buffer was adjusted to 7 before it was mixed with methanol. On each day, the strength of the mobile phase was prepared to achieve a retention time for bortezomib of about 15.5 min through a 25 cm × 4.6 mm reverse-phase C_{18}, 5-µm column (Symmetry, Waters Scientific, Toronto, Ontario) at 1.4 mL/min. Duplicate 10-µL quantities of each prepared sample, quality control samples, and standards were injected directly onto the column with an autoinjector (Ultra WISP 715, Waters Scientific, Toronto, Ontario).

The column effluent was monitored with a variable-wavelength ultraviolet detector (UV3000, Thermo Separation Products) at 270 nm. The signal from the detector was integrated and recorded with a chromatography data system (PC1000, Thermo Separation Products). The area under the bortezomib peak at 270 nm was subjected to least-squares linear regression, and the bortezomib concentration in each sample was determined by interpolation from the standard curve. This method is identical with the method reported by André and others[6] with respect to column, mobile phase, flow rate, and wavelength of detection. However, we did not use an internal standard, and our bortezomib retention time was slightly shorter (15.5 min) than that reported by the previous authors (17 min).[6]

Assay Validation

Following set-up of the chromatographic system for bortezomib, the suitability of this method for use as a stability-indicating assay was tested by accelerating the degradation of bortezomib with a variety of concentrations of sodium hypochlorite. The contents of a 3.5-mg vial of bortezomib (bortezomib mannitol boronic ester for injection, Velcade, Ortho Biotech, Division of Janssen Ortho Inc, lot 4CBS301, expiry March 2006) were dissolved in 3.5 mL of distilled water to prepare a 1 mg/mL solution. To 100-µL samples of this solution, 5-µL samples of various concentrations of sodium hypochlorite were added (sodium hypochlorite 1%, Hygeol, Wampole Canada, lot 0B030A, expiry February 2008; 1.00%, 0.80%, 0.70%, 0.50%, 0.40%, 0.30%, 0.25%, 0.20%, 0.10% and 0.01% solutions, prepared by dilution with distilled water). Each mixture was vortexed and chromatographed immediately. Chromatograms from all samples were inspected for the appearance of additional peaks, and the bortezomib peak was compared between samples for changes in concentration, retention time, and peak shape (electronic overlay and numeric calculation of tailing). Ultraviolet spectral purity of the bortezomib peak (200–365 nm, 6-nm bandwidth, deuterium lamp UV3000, Thermo Separation Products) in a chromatogram of a degraded sample produced by addition of sodium hypochlorite was compared with the spectrum of an authentic undegraded sample of bortezomib in water obtained at time 0. These chromatograms were also compared with validation chromatograms published by André and others.[6]

Following this first phase of evaluation and validation, the accuracy and reproducibility of standard curves were tested over 5 days, and system suitability criteria (theoretical plates, tailing, and retention time) were developed to ensure consistent chromatographic performance on each study day.[7] On the basis of considerations of the interday slope and assay variability for standards observed during assay validation, the quantitative resolution of the method was determined (0.0031 mg/mL), and bortezomib concentrations were then recorded to the nearest 0.01 mg/mL.

Stability Study

On study day 0, six 3.5-mg vials of bortezomib (Ortho Biotech, Division of Janssen-Ortho Inc, lot 4CBS301, expiry March 2006) were each reconstituted with 3.5 mL of 0.9% sodium NS to prepare solutions of concentration 1.0 mg/mL. Three of the vials were stored in the refrigerator and 3 were stored at room temperature, unprotected from fluorescent room light.

Physical Stability

On study days 0, 1, 4, 8, 11, 15, 18, 21, 28, 34, and 42, samples were drawn for analysis of concentration and were inspected visually, against a white and a black background, for changes in colour and presence of particulate matter.

Bortezomib Analysis

On study day 0, a 3.5-mg vial of bortezomib (Ortho Biotech, Division of Janssen-Ortho Inc, lot 4CBS301, expiry March 2006) was reconstituted with 3 mL of distilled water to make a solution with concentration 1.167 mg/mL. Aliquots of this solution were stored in a freezer at –75°C for the duration of the study period and were thawed as required. On each study day (0, 1, 4, 8, 11, 15, 18, 21, 28, 34, and 42), a 40-µL aliquot of this solution was thawed to prepare standards with final concentrations of 1.167, 0.875, 0.438, 0.219, and 0.146 mg/mL. When combined with a blank these standards allowed construction of a standard curve. Also, 2 quality control samples with bortezomib concentrations of 0.583 and 0.292 mg/mL were prepared from the same stock solution. On study day 21, a second 3.5-mg vial was reconstituted with 3 mL of distilled water. The standard curve prepared from this second vial was compared with the first one, and chromatograms were evaluated for differences in degradation products. Ten-microlitre quantities of each standard, each study sample, and each quality control sample were chromatographed in duplicate without dilution. Intraday and interday errors were assessed by the coefficients of variation of the peak areas of both quality control samples and standards.

On each study day (0, 1, 4, 8, 11, 15, 18, 21, 28, 34, and 42), samples drawn from each of the 3 vials stored at both temperatures were assayed for bortezomib concentration. All samples initially contained a nominal concentration of 1.0 mg/mL of bortezomib. Ten-microlitre quantities of each sample were injected directly onto the liquid chromatographic system without further preparation, in duplicate, to ensure the ability to distinguish concentrations in each vial that differed by 10%.[8,9]

Data Reduction and Statistical Analysis

After determining the coefficient of variation of the assay, a power calculation indicated that duplicate analysis of samples would distinguish between concen-

trations that differed by at least 10% within each individual container.[8,9] Means were calculated for replicate analyses. Mean results from different days for each test were compared statistically to determine if there was an association between the observed result and time. Simple linear regression and multiple linear regression were used to determine if there was an association between the observed concentration and study day and/or temperature. The 95% CI of the percent remaining on the last study day was calculated for each vial held at 4°C and 23°C. Analysis of variance (ANOVA) was used to test differences in concentration on different study days and at different temperatures. The 5% level (by Fisher's least significant difference test) was used as the a priori cutoff for significance. Bortezomib concentrations were considered "acceptable" or "within acceptable limits" if the lower limit of the 95% confidence interval of concentration remaining was greater than 90% of the initial (day 0) concentration.

RESULTS

Accelerated Degradation and Assay Validation

Degradation of bortezomib with sodium hypochlorite occurred quickly. At 23°C, a 1.0-mg/mL solution of bortezomib in water degraded to 5.92% of the original concentration when 5 µL of a 0.5% solution of sodium hypochlorite was added. Solutions with lower concentrations of sodium hypochlorite degraded bortezomib more slowly. When 5 µL of a 0.25% solution of sodium hypochlorite was added and the sample was chromatographed immediately, 40.65% of the original concentration remained. These solutions had degradation products of bortezomib that eluted at 4.3 and 13.5 min (Figure 1). Additional peaks eluted at 29 min and between 4 and 9 min when solutions with concentrations of sodium hypochlorite above 0.4% were added. None of these degradation products interfered with bortezomib quantification, and the ultraviolet spectrum of the bortezomib peak (200–365 nm) in a degraded sample was no different than the spectrum of the authentic undegraded standard. The chromatograms of bortezomib with sodium hypochlorite were virtually identical with chromatograms of bortezomib with hydrogen peroxide published by André and others.[6] Hydrogen peroxide and sodium hypochlorite generated all of the degradation products typically produced by acid, base, or heat, as well as 2 other degradation products, which eluted at 13.5 and 29 min in the system described here.

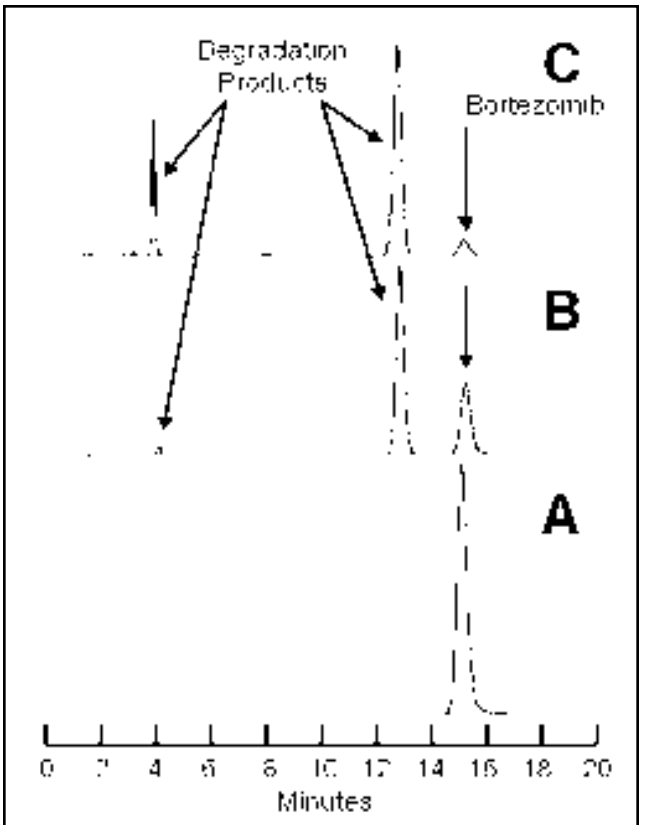

Figure 1. Chromatogram A represents a solution of 1.0 mg/mL bortezomib in water before addition of sodium hypochlorite. Chromatogram B represents a sample that was chromatographed immediately after the addition of 5 µL of 0.3% sodium hypochlorite (29% of original quantity remains). Chromatogram C represents a sample that was chromatographed immediately after the addition of 5 µL of 0.4% sodium hypochlorite (12% remains). Degradation products appeared at 4.3 and 13.5 min; additional products appeared at 4.3, 4.8, 8.7, and 29 min (not evident in chromatogram).

The chromatographic separation of these degradation products from bortezomib and the similarity of the ultraviolet spectrum (200–365 nm) between an authentic standard and bortezomib in a degraded sample led to the conclusion that this analytical method was suitable for indicating stability.[3-5]

Analysis of standard curves and quality control samples during validation indicated that the bortezomib concentration was measured accurately. Standards and quality control samples over the study period showed an average absolute deviation of 2.12% from the expected concentration. Between-day variation in the slope (as determined by coefficient of variation [CV%]) averaged 5.2%. Analytical error with replicate measurement (as measured by CV) averaged 0.78% within a day and

Table 1. Observed Concentration of Bortezomib Remaining after Storage in Vials at 4°C and 23°C*

Study Day	Refrigerated (4°C)	Room Temperature (23°C)
Initial concentration (mg/mL)	1.02	1.04
Day 1	98.12±1.08	99.21±0.59
Day 4	98.27±1.19	100.19±1.22
Day 8	98.92±0.99	99.04±1.97
Day 11	100.05±1.53	100.78±2.43
Day 15	100.62±3.17	102.05±1.81
Day 18	98.50±1.18	99.18±1.22
Day 21	102.20±0.53	101.13±1.91
Day 28	100.06±0.74	100.03±2.71
Day 34	100.41±1.28	100.02±1.52
Day 42	100.72±0.83	100.02±2.27
% remaining on day 42†	101.06	100.36
Lower limit of 95% CI for degradation rate (fastest degradation rate) (% per day)	–0.00801	–0.04077
Lower limit of 95% CI for % remaining on day 42‡	99.66	98.29

CI = confidence interval.

*Concentrations are expressed as mean percent remaining ± standard deviation. The percentage remaining was calculated on the basis of concentration determined in duplicate for each of 3 replicate vials stored at each temperature, relative to the concentration on study day 0.

†Percent remaining on day 42 is based on linear regression. The concentrations on day 42 and on day 0 were also determined by linear regression. Calculation: (concentration on day 42 ÷ concentration on day 0) x 100.

‡Calculated using the lower limit of the 95% CI of the slope, determined by linear regression, and an initial concentration of 100%. Calculation: (100 x {[day 0 concentration + (slope x 42 days)]/day 0 concentration}), where day 0 concentration is taken as 100%.

2.06% between days. These results indicate that differences of 10% or more can be confidently detected within individual containers with acceptable error rates.[7,8]

Bortezomib Stability Study

All solutions, as reconstituted in the original manufacturer's glass vials, were initially clear and colourless and remained so for the duration of the study. No visible particles were observed in any solution throughout the study period.

During the study period, the concentrations in all study samples at both temperatures retained at least 98.12% of the initial concentration (Table 1). Over the 42-day study period, the bortezomib concentration varied between days (as assessed by CV), by 0.9% for vials held at 4°C and by 1.25% for vials kept at room temperature.

ANOVA revealed no significant difference in the percent remaining between vials stored at different temperatures but showed that a difference of only 0.5% between any 2 study days was statistically significant. However, linear regression did not reveal a significant linear trend for the concentration to change during the study period for vials stored at 4°C ($p = 0.71$) or room temperature ($p = 0.08$). On day 42, the lowest concentration, based on the fastest degradation rate (with 95% confidence), was calculated to be 99.66% for vials stored at 4°C and 98.29% for vials stored at room temperature. Inspection of chromatograms during the stability study (Figure 2) revealed small amounts of degradation products in solutions that had been stored at room temperature for 42 days.

DISCUSSION

Demonstration of a trend or a consistent decline in concentration during the study was considered more important than demonstrating a statistical difference in concentration between any 2 days. In fact, whereas significant differences between concentrations on any 2 study days were observed ($p = 0.012$), these random fluctuations in concentration around the initial concentration are minor and of no practical importance and should be considered "noise" or experimental error. During the study period, concentrations observed in all study samples at both temperatures remained within 2.5% of the initial concentration. The concentration

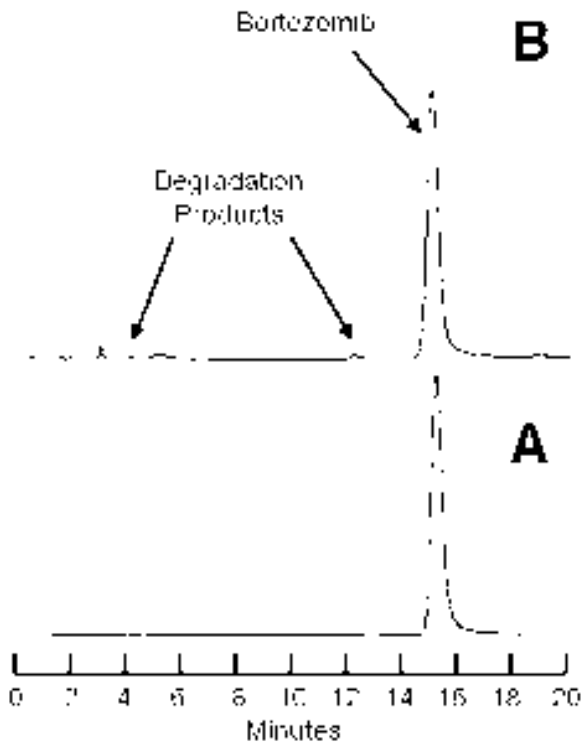

Figure 2. Chromatograms A and B represent a 1.0 mg/mL bortezomib solution, as reconstituted with 0.9% sodium chloride in the manufacturer's original glass vial and stored at 23°C during the stability study. Chromatogram A: Study day 0. Chromatogram B: After 42 days storage at room temperature. Very small amounts of degradation products, as observed during the accelerated degradation study, were observed in solutions stored at room temperature.

estimated by linear regression was within 1% of the initial concentration on day 42, and the lower limit of the 95% CI of the percent remaining on day 42 was within 2% of the initial (day 0) concentration.

Because only small changes in bortezomib concentration were detected under these storage conditions, assurance of the specificity of the analytical method is very important. This specificity was demonstrated during the accelerated degradation studies (Figure 1). In those studies, reductions in bortezomib concentration were measured as the concentrations of apparent degradation products increased. The separation and detection of intact drug in the presence of degradation compounds must be assured before the method can be considered stability-indicating.[3-5]

As described earlier, André and others[6] recently published a bortezomib stability study in which they used solution remaining in vials after preparation of patient doses as their study samples. These authors reported that syringes containing 1 mg/mL of bortezomib stored for 5 days at 5°C had 95% of the original concentration remaining; corresponding values were 91% for syringes stored at 22°C and 66% for syringes stored at 60°C.[6] The method used by André and others[6] was very similar to the one used in the current study, except for a small difference in retention time and the absence of an internal standard in the current study; as such, it would seem that the apparently greater rates of loss of concentration reported by André and others[6] cannot be explained by their analytical method. The bortezomib retention times in the chromatograms reported by André and others[6] varied between 15.6 and 18 min, and their internal standard, quinine, was reported to elute at 23 min. This is very close to the degradation product reported to elute at 30 min, given variations in retention time and the fact that both of these peaks take more than 3 minutes to elute. Co-elution of a degradation product and the internal standard would produce concentrations that are falsely low. André and others[6] did not publish chromatograms of samples from their stability study, and it is therefore not possible to evaluate if degradation products were present in solutions observed to have losses of more than 10% during storage at 5°C or 22°C. It is also not possible to evaluate if these degradation products interfered with the internal standard, and the authors made no statement about the appearance of degradation products in stored samples.[6] Furthermore, although the data published by André and others[6] demonstrated stability over the first 5 days at 5°C, this was followed by a more rapid decline in concentration between days 8 and 11. Deviations between the observed data and the amount estimated to remain by linear regression appeared to double for day 8 (syringes) and day 11 (vials). Once concentrations dropped below 90% in the solutions stored at 5°C, no further analysis was performed. Therefore, it is not possible to evaluate if the results observed on the last study day for samples stored at 5°C were lower than expected.

André and others[6] reported that bortezomib is particularly sensitive to oxidation, and this is evident by the effect on bortezomib stability of sodium hypochlorite in the current study and of hydrogen peroxide, as reported by André and others.[6] The nitrogen within the Velcade vial limits oxidation until reconstitution, but Velcade itself contains no antioxidant to limit oxidation after reconstitution. André and others[6] reported that air was not removed from the vials used in

their study. However, they used solution that remained in vials after preparation of patient doses, and it is therefore possible that a greater amount of oxygen was introduced into their vials relative to those used in the current study and that oxygen might have contributed to degradation. Nonetheless, it is our experience that degradation due to oxygen is a slow process and does not generally result in losses approaching 1% per day at 5°C or even 23°C.

We conclude that bortezomib solutions of 1 mg/mL, stored in the manufacturer's vial for up to 42 days at 4°C or at room temperature, are stable and retain more than 98% of the initial bortezomib concentration during the storage period.

Note added in proof: As of September 2007, the product monograph for bortezomib states that, after reconstitution, the drug may be stored for up to 8 h in a vial or syringe. The change to the monograph was made after this paper was accepted for publication.

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ON THE FRONT COVER

Echinacea purpurea

The photograph on the front cover depicts *Echinacea purpurea* (commonly known as the purple coneflower). It was taken by Michael Wong in August 2006 with a Nikon D50 dSLR equipped with a 50-mm lens and close-up filter attachments. The setting was the garden outside the head office of Freeman Formalwear, where Michael was waiting for his groomsmen to arrive so they could try on tuxedos for Michael's wedding.

Echinacea purpurea, a hardy perennial plant, is native to the open plains of the United States and does well even in very cold climates. *Echinacea* has traditionally been taken to stimulate the body's immune system and to prevent infections such as the common cold. These purported benefits may be related to the phenols chichoric, caftaric, and echinacoside. However, the effects of *Echinacea* on the immune system are controversial. In a recent randomized controlled study of volunteers exposed to rhinovirus (*N Engl J Med* 2005;353[4]:341-348), there was no difference in rates of infection or severity of symptoms between volunteers given an echinacea preparation and those given placebo.

CJHP would be pleased to consider photographs of medicinal plants taken by CSHP members for use on the cover of the Journal. If you would like to submit a photograph, please send an electronic copy (minimum resolution 300 dpi) to Sonya Heggart at sheggart@cshp.ca