

# Extended Stability of Pantoprazole for Injection in 0.9% Sodium Chloride or 5% Dextrose at 4°C and 23°C

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## ABSTRACT

**Background:** The pantoprazole product available in Canada for IV administration has recently been reformulated to include ethylenediaminetetra-acetic acid (EDTA). The purpose of this study was to determine if the chemical stability of pantoprazole for injection containing EDTA (PANTO IV), admixed in polyvinyl chloride (PVC) minibags at concentrations of 0.16 mg/mL and 0.80 mg/mL in 5% dextrose in water (D5W) or 0.9% sodium chloride for injection (normal saline [NS]) and stored at 4°C or 23°C, could be extended beyond the manufacturer's expiry period of 24 hours.

**Methods:** Sodium pantoprazole was reconstituted in NS or D5W, and 32 PVC minibags were prepared, 16 containing pantoprazole at a nominal concentration of 0.16 mg/mL (8 in NS, 8 in D5W) and 16 containing pantoprazole at a nominal concentration of 0.80 mg/mL (8 in NS, 8 in D5W). Half of the minibags for each diluent-concentration combination were stored at 4°C and half at room temperature (23°C). The concentration of pantoprazole in each minibag was determined by a validated, stability-indicating liquid chromatographic method on study days 0, 1, 2, 4, 7, 9, 11, 14, and 21.

**Results:** Analysis of variance revealed differences in the percentage of drug remaining in relation to temperature ( $p < 0.001$ ), study day ( $p = 0.001$ ), concentration ( $p = 0.007$ ), and diluent ( $p = 0.008$ ).

**Conclusions:** Solutions of pantoprazole in D5W with concentration between 0.16 mg/mL and 0.80 mg/mL can be stored for a maximum of 11 days at 4°C plus an additional 6 h at 23°C. The saline solutions degraded more slowly, and pantoprazole admixtures in NS with concentration between 0.16 mg/mL and 0.80 mg/mL can be stored for 20 days at 4°C plus an additional 6 h at 23°C. Under these conditions, more than 90% of the initial concentration will remain (with 95% confidence).

**Key words:** pantoprazole, drug stability

## RÉSUMÉ

**Objectifs :** Le pantoprazole commercialisé au Canada pour administration intraveineuse a récemment été modifié pour inclure dans sa composition de l'acide éthylène diamine tétra acétique (EDTA). Le but de cette étude était de déterminer si la stabilité chimique du pantoprazole pour injection contenant de l'EDTA (Panto IV), mélangé dans des minisacs de polychlorure de vinyle (PVC) à des concentrations de 0,16 mg/mL et de 0,80 mg/mL dans du dextrose à 5 % dans l'eau (D5E) ou du chlorure de sodium à 0,9 % pour injection (solution physiologique salée [SPS]) qui ont été entreposés à 4 °C ou à 23 °C, pouvait se prolonger au-delà de la période de 24 heures stipulée par le fabricant.

**Méthodes :** Le pantoprazole sodique a été reconstitué dans de la SPS ou du D5E et 32 minisacs de PVC ont été préparés, 16 contenant du pantoprazole à une concentration nominale de 0,16 mg/mL (8 dans de la SPS, 8 dans du D5E) et 16 contenant du pantoprazole à une concentration nominale de 0,80 mg/mL (8 dans de la SPS, 8 dans du D5E). La moitié des minisacs de chaque combinaison diluant-concentration ont ensuite été entreposés à une température de 4 °C et l'autre moitié, à la température ambiante (23 °C). La concentration de pantoprazole dans chaque minisac a été déterminée à l'aide d'une épreuve validée par chromatographie liquide mesurant la stabilité aux jours 0, 1, 2, 4, 7, 9, 11, 14 et 21 de l'étude.

**Résultats :** L'analyse de variance a révélé des différences dans le pourcentage de médicament résiduel en fonction de la température ( $p < 0,001$ ), du jour de l'étude ( $p = 0,001$ ), de la concentration ( $p = 0,007$ ), et du diluant ( $p = 0,008$ ).

**Conclusions :** Les solutions de pantoprazole dans du D5E à des concentrations de 0,16 mg/mL ou de 0,80 mg/mL pourraient être conservées pendant un maximum de 11 jours à une température de 4 °C et pendant six heures supplémentaires à une température de 23 °C. Les solutions préparées dans de la SPS se sont dégradées plus lentement, et les mélanges de pantoprazole dans de la SPS à des concentrations de 0,16 mg/mL ou de 0,80 mg/mL pourraient être conservés pendant 20 jours à une température de 4 °C et pendant six heures supplémentaires à une température de 23 °C. Dans ces conditions, les solutions ont conservé plus de 90 % de leur concentration initiale de pantoprazole (intervalle de confiance à 95 %).

**Mots clés :** pantoprazole, stabilité des médicaments

[Traduction par l'éditeur]

## INTRODUCTION

The expiry date of medications intended for IV administration following reconstitution or dilution is often limited to about 24 h, even when data on extended stability exist, because of the potential for breaks in sterility and contamination of the product. However, when reconstitution and dilution are carried out in a sterile environment, based on the guidance of USP (United States Pharmacopeia) chapter <797> recommendations,<sup>1</sup> it is entirely reasonable to assign beyond-use dates of up to 14 days for low-risk compounded sterile products.<sup>2</sup> For many drugs, extending the beyond-use date may reduce wastage<sup>3,4</sup> and result in significant cost savings.

Pantoprazole is the first proton pump inhibitor for IV administration marketed in Canada. It is indicated when a rapid reduction in secretion of gastric acid is required for patients who cannot tolerate oral medications and was approved for the treatment of Zollinger–Ellison syndrome in 2002.<sup>5</sup> It is also administered by infusion to control acute upper gastrointestinal bleeding,<sup>6,7</sup> although it is not approved for this indication.

The pantoprazole product currently licensed in Canada for IV administration (PANTO IV) has recently been reformulated with ethylenediaminetetra-acetic acid (EDTA) to extend its stability beyond that of the original formulation. Previous publications on compatibility<sup>8</sup> and stability<sup>9,10</sup> relate to the original product, which did not contain EDTA. In fact, Ekpe and Jacobsen<sup>10</sup> evaluated the stability of pantoprazole in a variety of laboratory-grade buffers, and that report is therefore not useful for predicting or estimating the stability of the drug in commonly used IV solutions. The current Canadian product monograph for PANTO IV recommends that admixtures be used within 24 h following reconstitution and dilution.<sup>11</sup> To the authors' knowledge, no data have been published on the stability of the new formulation (containing EDTA).

The objective of this study was to evaluate, using a validated, stability-indicating, liquid chromatographic method, the stability of the new formulation of pantoprazole (PANTO IV) following reconstitution to a concentration of 4 mg/mL and further dilution with either 5% dextrose in water injection (D5W) or 0.9% sodium chloride (normal saline [NS]) to achieve concentrations of 0.16 mg/mL and 0.8 mg/mL. A concentration of 0.16 mg/mL is equivalent to 40 mg diluted in 250 mL, and a concentration of 0.8 mg/mL is equivalent to 40 mg in 50 mL or 200 mg in 250 mL. This concentration range encompasses all concentrations generally encountered in clinical practice and previously reported in compatibility<sup>8,12</sup> and stability<sup>9</sup> studies.

## METHODS

### Liquid Chromatographic Method

The liquid chromatographic system consisted of an isocratic solvent delivery pump (model P4000, Thermo

Separation Products, San Jose, California), which pumped a mixture of 30% acetonitrile (OmniSolv, EMD Chemicals Inc, Gibbstown, New Jersey) and 0.05 mol/L phosphate dibasic (catalogue no. S-9390, Sigma Chemical Co, St Louis, Missouri), adjusted to pH 7.1 with phosphoric acid (catalogue no. P286, Fisher Scientific, Toronto, Ontario), through a 15 cm × 4.6 mm reverse-phase 3 µm column (ABZ+plus, Supelco, Oakville, Ontario) at 1.0 mL/min. The samples (2 µL each) were introduced into the liquid chromatographic system using an auto injector (WISP 712, Waters Scientific, Toronto, Ontario).

The column effluent was monitored with a variable-wavelength ultraviolet detector (UV6000, Thermo Separation Products) at 280 nm. The signal from the detector was integrated and recorded with a chromatography data system (ChromQuest, Thermo Separation Products). The area under the pantoprazole peak at 280 nm was subjected to least-squares linear regression, and the pantoprazole concentration in each sample was determined by interpolation from the standard curve. This method is similar to the reverse-phase stability-indicating method previously described,<sup>9</sup> but with a different flow rate.

### Assay Validation

Following development of the chromatographic system for pantoprazole, the suitability of this method for use as a stability-indicating assay was tested by running samples of pantoprazole that had been subjected to accelerated degradation. Ten milligrams of pantoprazole (pantoprazole sodium for injection, PANTO IV, Altana–Nycomed, Oakville, Ontario; lot 370051, expiry January 2009; certificate of analysis: 0.14% impurities and 39.6 mg of pantoprazole per 40-mg vial or 99% of label claim) was dissolved in 10 mL of water to produce a 1 mg/mL solution. This was further diluted with water and HCl 5 mol/L to prepare a 0.5 mg/mL solution of pantoprazole at pH 4. The solution was placed in a glass vial, and samples were drawn immediately and at 18 other times over a 570-min period while the sample was kept at room temperature (23°C). The samples were chromatographed, and the chromatograms were inspected for the appearance of additional peaks. The pantoprazole peak was compared between samples for changes in concentration, retention time, peak shape, and ultraviolet spectral purity compared to an authentic undegraded standard containing only 0.14% impurities.

Following this first phase of evaluation and validation, the accuracy and reproducibility of standard curves were tested over 4 days, and system suitability criteria (theoretical plates, tailing, and retention time) were developed to ensure consistent chromatographic performance. Standard curves were prepared daily by weighing an exact amount of at least 10 mg of sodium pantoprazole (pantoprazole sodium for injection, PANTO IV,

same source as described above) to prepare a 1 mg/mL stock solution of pantoprazole. Samples of this stock solution were further diluted to obtain standards with final concentrations of 0.063, 0.188, 0.375, 0.750, and 1.00 mg/mL. These standards were combined with a blank to construct a standard curve. A 2- $\mu$ L volume of each standard was chromatographed in duplicate. Also, 3 quality control samples of pantoprazole (concentrations 0.500, 0.375, and 0.125 mg/mL) were chromatographed in duplicate each day. The concentration of pantoprazole in these quality control samples was determined and compared to the known concentrations. Intraday and interday errors were assessed by the coefficients of variation of the peak areas of both the quality control samples and the standards.

### Stability Study

On study day 0, twenty 40-mg vials of pantoprazole (sodium pantoprazole, PANTO IV, Altana–Nycomed; lot 370051, expiry January 2009) were reconstituted according to the manufacturer's instructions with 10 mL of NS and were then further diluted with either NS (50-mL PVC minibags; Hospira, Montréal, Quebec; lot 49-016-NA, expiry July 2008) or D5W (50-mL PVC minibags; Baxter Corporation, Toronto, Ontario; lot P199117, expiry June 2008) to prepare 32 PVC minibags containing pantoprazole with a nominal concentration of either 0.16-mg/mL (8 bags with each diluent) or 0.80-mg/mL (8 bags with each diluent).

For the minibags containing 0.80 mg/mL of pantoprazole, bag overfill (assumed to be 8 mL) and a volume of diluent equal to the volume of pantoprazole added (10 mL) were removed before addition of the 10-mL portion of pantoprazole 4 mg/mL solution, such that the final concentration approximated as closely as possible 0.80 mg/mL. Eight PVC minibags containing pantoprazole 0.80 mg/mL diluted in NS and 8 PVC minibags containing pantoprazole 0.80 mg/mL diluted in D5W were prepared. Four minibags of each solution were stored at room temperature (23°C) unprotected from ambient fluorescent room light, and 4 minibags of each solution were stored in the refrigerator (4°C).

For the minibags containing 0.16-mg/mL of pantoprazole, bag overfill (assumed to be 8 mL) and a volume of diluent equal to the volume of pantoprazole added (2 mL) were not removed before addition of the 2-mL portion of pantoprazole 4 mg/mL solution. Eight PVC minibags containing pantoprazole 0.16 mg/mL diluted in NS and 8 PVC minibags containing 0.16-mg/mL pantoprazole diluted in D5W were prepared. Four minibags of each solution were stored at room temperature (23°C), unprotected from ambient fluorescent room light and 4 minibags of each solution were stored in the refrigerator (4°C).

For each solution, pantoprazole concentration was measured and a physical inspection was completed on study

days 0, 1, 2, 4, 7, 9, 11, 14, and 21. The drug concentration was determined by the validated, stability-indicating, liquid chromatographic method described above.

On each analysis day, a 2-mL sample was drawn from each minibag. Samples for chromatographic analysis with a nominal concentration of 0.16 mg/mL were injected directly onto the column without prior dilution. Samples with a nominal concentration of 0.80 mg/mL were diluted 2-fold by mixing 0.2 mL of the sample drawn from the PVC minibag with 0.2 mL of distilled water.

### Data Reduction and Statistical Analysis

After calculation of the coefficient of variation for replicate determinations of concentration for an assay, a power calculation demonstrated that 2 replicates were required to ensure that the analytical method could distinguish between concentrations differing by at least 10%.<sup>13,14</sup> Means were calculated for replicated analyses, and these values are reported in the summary tables. Mean results from different days for each test were compared statistically (by linear regression) to determine if there was an association between the observed result and time. The slope of the relationship between the percent remaining and study day, determined by linear regression, was accepted as the degradation rate (%/day). The lower limit of the 95% confidence interval (CI) of this slope was also calculated, as it represents the fastest degradation rate with 95% confidence. Analysis of variance was used to test differences in degradation rate between various combinations of study day, temperature, diluent, and concentration. The 5% level was used as the a priori cutoff for significance. Concentrations were considered "acceptable" or "within acceptable limits" if (1) the measured concentration on the specified study day was greater than 90% of the initial concentration (day 0) and (2) the concentration on the study day exceeded 90% of the initial concentration (day 0) with 95% confidence.

## RESULTS

### Accelerated Degradation and Assay Validation

Degradation of a 0.5 mg/mL solution of pantoprazole in water at room temperature (23°C) after acidification to pH 4 with 5 mol/L HCl occurred relatively quickly, such that less than 2.5% of the initial concentration remained after 570 min. At least 3 degradation products were observed in chromatograms (Figure 1). None of these degradation products interfered with quantification of pantoprazole. As a result of the chromatographic separation of these degradation products from pantoprazole and the similarity of the UV spectrum (200–320 nm) between an authentic pantoprazole standard

and the pantoprazole in a degraded sample, it was concluded that this analytical method was stability-indicating.<sup>15-17</sup>

Assay validation demonstrated that deviation from the known concentration on any day averaged 2.75%. Within-day replicate error averaged 1.35%, whereas between-day replicate error averaged less than 2.61%.

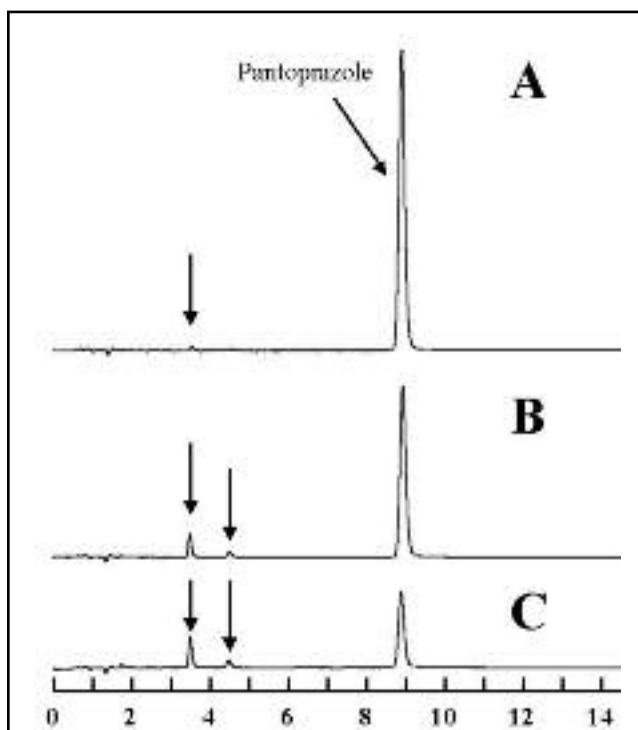
Analyses of accuracy and reproducibility during the study period indicated that pantoprazole concentrations were measured accurately and reproducibly. Accuracy, based on the mean of duplicate determinations of the standards over the study period, averaged 2.08% deviation from the expected concentration. During the study period, within-day replicate error (measured by the coefficient of variation) averaged 1.37% for the standards and 1.17% for the quality control samples. Between-day replicate error (as measured by the coefficient of variation) averaged 2.97% for the standards and 3.16% for the quality control samples. These results indicate that differences of 10% or more could be confidently detected with acceptable

error rates<sup>13,14</sup> with duplicate analysis. System suitability criteria were developed on the basis of daily calculations of theoretical plates, tailing, retention time, and accuracy observed during the validation period and were used to ensure continued chromatographic performance during the study period.

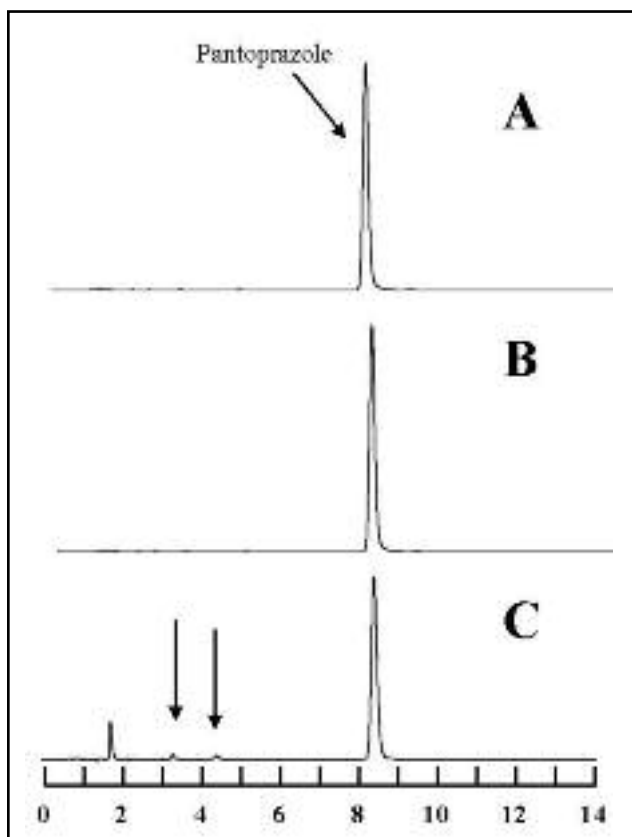
### Pantoprazole Stability in PVC Minibags

The initial concentration and the observed percentage remaining on each study day for each pantoprazole solution are listed in Table 1. The observed initial concentrations were about 0.15 mg/mL and 0.88 mg/mL. This indicates that the overfill in the PVC minibags was closer to 3 mL, rather than the assumed overfill of 8 mL.

Analysis of variance revealed differences in percentage remaining in relation to temperature ( $p < 0.001$ ), study day



**Figure 1.** Chromatogram A represents a solution of pantoprazole 0.5 mg/mL in water, pH 4, at time 0. After 30 min at room temperature, 56% of the initial concentration remained (chromatogram B), and after 120 min, 25% of the initial concentration remained (chromatogram C). The pantoprazole eluted at 9 min. Arrows indicate unidentified degradation products. A third, unidentified degradation product was observed after 210 min of storage. This degradation product eluted at 7 mins (not shown). The peaks for all degradation products were well separated from the peak for pantoprazole.



**Figure 2.** Chromatograms observed during the stability study. A: Pantoprazole 0.8 mg/mL in 0.9% sodium chloride on study day 0. B: Pantoprazole 0.8 mg/mL in 0.9% sodium chloride after 14 days of storage at 4°C. C: Pantoprazole 0.8 mg/mL solution after 14 days of storage at room temperature (86% of the initial pantoprazole concentration remaining). Degradation products are identified by arrows. These degradation products had identical retention times to those observed in the accelerated degradation study (pH 4, room temperature; see Figure 1).

**Table 1. Percentage of Pantoprazole Remaining\* after Storage at 4°C and Room Temperature**

Variable	Nominal Concentration 0.16 mg/mL				Nominal Concentration 0.80 mg/mL			
	D5W		NS		D5W		NS	
	23°C	4°C	23°C	4°C	23°C	4°C	23°C	4°C
<b>Initial measured concentration (mg/mL)</b>	0.15±0.01	0.15±0.01	0.15±0.01	0.15±0.01	0.89±0.01	0.88±0.03	0.88±0.01	0.89±0.02
<b>% of original concentration remaining*</b>								
Study day 1	90.11±2.58	96.66±3.60	98.11±2.12	100.09±1.32	97.61±2.53	102.42±2.15	104.13±1.56	103.93±1.31
Study day 2	87.35±5.00	95.85±4.43	94.01±0.54	97.58±1.43	93.59±4.31	99.57±2.76	101.09±2.33	102.29±3.32
Study day 4	70.89±4.31	96.59±2.79	89.44±1.15	99.76±2.78	91.28±3.44	103.27±1.92	99.86±3.96	106.81±2.87
Study day 7	52.45±4.14	97.36±1.89	81.37±0.80	97.42±2.31	81.29±2.48	102.18±1.47	95.61±2.31	105.46±3.51
Study day 9	52.38±3.65	102.35±4.15	79.91±3.16	104.74±1.51	72.56±3.73	94.44±5.62	89.19±2.83	96.89±1.19
Study day 11	30.79±7.07	97.12±2.51	64.26±3.48	103.52±4.12	73.60±3.01	106.36±3.43	95.45±3.09	110.80±4.33
Study day 14	19.89±9.95	94.64±3.03	46.88±1.48	101.08±2.10	62.78±3.12	106.19±3.26	86.87±1.59	107.10±0.99
Study day 21	5.90±15.96	89.29±3.44	19.49±2.89	95.52±2.53	36.19±5.05	99.28±2.32	64.53±2.70	103.67±1.17
<b>Degradation rate† (%/day)</b>	-4.685	-0.324	-3.837	-0.050	-2.933	0.043	-1.621	0.153
<b>T-90%‡ (days)</b>	0.55	28.18	3.71	205.85	3.84	261.24	9.50	84.68
<b>Fastest degradation rate (%/day) (lower limit of 95% CI)‡</b>	-6.44	-0.69	-4.46	-0.43	-3.27	-0.44	-2.21	-0.36
<b>% remaining based on fastest degradation rate (95% CI of regression)§</b>								
Study day 1	94.36	99.31	95.54	99.57	96.73	99.56	97.80	99.64
Study day 2	88.72	98.62	91.08	99.15	93.46	99.12	95.59	99.27
Study day 3	83.07	97.93	86.61	98.72	90.19	98.69	93.38	98.91
Study day 7	60.51	95.18	68.77	97.01	77.11	96.93	84.56	97.46
Study day 14	21.01	90.35	37.53	94.01	54.22	93.86	69.13	94.92
Study day 21	-	85.53	6.30	91.02	31.34	90.80	53.69	92.38
<b>T-90% (days), based on fastest degradation rate (lower limit of 95% CI)</b>	1.55	14.51	2.24	23.38	3.06	22.82	4.53	27.55
<b>Estimated % remaining,¶ using fastest degradation rate (lower limit of 95% CI)</b>								
11 days at 4°C + 8 h at 23°C		90.27		93.81		94.09		95.27
10 days at 4°C + 28 h at 23°C				90.52				93.80
20 days at 4°C + 6 h at 23°C				90.33				92.19

CI = confidence interval, D5W = 5% dextrose in water, NS = 0.9% sodium chloride (normal saline), T-90% = time for initial concentration to decline by 10% based on calculated degradation rate.

\*Each value is a mean based on duplicate determination of 3 samples ± standard deviation. The percent remaining is based on the observed concentration on day 0 (100%).

†The degradation rate was determined by linear regression of percent remaining on each study day.

‡Fastest degradation rate and T-90% are based on the lower limit of the 95% CI of the regression-determined slope.

§Percent remaining is based on an initial concentration of 100% and the fastest degradation rate determined by regression.

¶The fastest observed degradation rates determined by regression (95% CI) were used in calculations for a solution stored in a polyvinyl chloride minibag at 4°C followed by storage for an additional period at room temperature.

( $p = 0.001$ ), concentration ( $p = 0.007$ ), and diluent ( $p = 0.008$ ). Both diluent and concentration had an effect on degradation, as indicated by the calculated degradation rates, which were greater for the lower nominal concentration of 0.16 mg/mL in D5W. The greatest rate of loss, 4.685% per day, was observed for concentration 0.16 mg/mL in D5W stored at room tem-

perature; the rate of loss was 3.837% per day for concentration 0.16 mg/mL in NS stored at room temperature and 2.933% per day for 0.80 mg/mL in D5W stored at room temperature.

Solutions stored at 23°C degraded between 7- and 70-fold faster than comparable solutions and concentrations stored at 4°C. At 4°C, the observed rate of loss varied between 0.36%

and 0.69% per day. The greatest loss was observed for the 0.16 mg/mL solution in D5W, for which 94.64% of the initial concentration remained on day 14. For solutions with less than 90% of the initial concentration remaining, the degradation products found during the accelerated degradation studies were observed.

Linear regression based on the fastest degradation rate with 95% confidence predicted that solutions of pantoprazole diluted in D5W or NS and stored at 23°C will retain 90% of the initial concentration for at least 1.5 days (range of lower limit of 95% CI 1.55–4.53 days; Table 1). Linear regression based on the fastest degradation rate indicated that solutions of pantoprazole diluted in D5W or NS and stored at 4°C will retain 90% of the initial concentration for at least 14.5 days (range of lower limit of 95% CI 14.51–27.55 days; Table 1).

## DISCUSSION

In this study, the stability of pantoprazole solutions stored for up to 21 days in PVC minibags was affected by temperature (with faster degradation at room temperature than at 4°C), diluent (with greater degradation in D5W than in NS), and concentration (with greater rate of degradation, expressed as percent per day, with the 0.16 mg/mL preparations than with the 0.80 mg/mL solutions).

Previous publications on the stability of pantoprazole solutions<sup>9,10</sup> tested the original product, which did not contain EDTA. In fact, Ekpe and Jacobsen<sup>10</sup> investigated the stability of pantoprazole in a variety of laboratory-grade buffers, and their results are therefore not useful for predicting stability of the drug in commonly used IV solutions. Nevertheless, in an earlier study of pantoprazole stability in NS (published in abstract form),<sup>9</sup> pantoprazole was judged to be stable for 14 days at 4°C or 48 h at 23°C. The stability of pantoprazole in NS observed in the current study is consistent with the previously reported study.

It is currently accepted practice to base beyond-use dates on the shortest period determined from a 95% CI from the data. The 95% CI takes into account uncertainty in the data, which may be related to a variety of factors.<sup>18</sup> The most obvious factor is analytical error, but lot-to-lot variation, a relationship between degradation rate and the number of time points or sampling days in the study design, and other minor random errors (such as fluctuations in storage temperature) generally go unnoticed and could contribute to a greater or lesser degree of degradation observed in a PVC bag. Using a 95% CI makes the beyond-use date more conservative, which provides some measure of certainty that medication delivered to a patient has not yet expired, even if there are minor delays in delivering the medication to the ward or in the time taken to hang or administer the bag if the patient is not in his or her room at administration time, or delays due to other realities of the

**Table 2. Summary of Chemical Stability of Pantoprazole (0.16 to 0.8 mg/mL)\* for Injection Stored in Polyvinyl Chloride Minibags**

Diluent	Storage Temperature (°C)	Chemical Stability†‡
D5W	23	24 h
	4	11 days + 8 h at 23°C
NS	23	48 h
	4	20 days + 6 h at 23°C‡
	4	11 days + 28 h at 23°C

D5W = dextrose 5% in water, NS = normal saline (0.9% sodium chloride).

\*This concentration range encompasses the concentrations used in the clinical setting, from 40 mg/250 mL to 40 mg/50 mL (the latter being equivalent to 200 mg/250 mL).

†Defined in this study as at least 90% of initial pantoprazole concentration remaining after storage under the specified conditions.

‡USP (United States Pharmacopeia) chapter <797>

recommends that low-risk compounded sterile preparations shall not be stored for longer than 14 days under refrigeration.<sup>1</sup>

hospital environment, medication administration, and patient life. Using a beyond-use date that is based on the 95% CI means that there is only a 2.5% chance that the true expiry date is actually less than our recommended date of 20 days at 4°C plus an additional 6 h at room temperature. Use of the estimated T-90% from the observed data in NS solutions (205.85 and 261.24 days; Table 1) does not take uncertainty into account and could place patients at risk, since the T-90% falls well beyond the observation period of the study. It is our belief that the beyond-use date of a product should never be extended, for the sake of convenience, on the basis of time-related or financial considerations. Financial gains realized through reduction in wastage will be minimal with beyond-use dates of 7 days or longer,<sup>1,2</sup> and a beyond-use date exceeding this time increases the risk to the patient with only marginal incremental financial benefit.

Based on the fastest degradation rate, determined with 95% confidence, solutions of pantoprazole in concentrations ranging from 0.16 mg/mL to 0.80 mg/mL diluted in D5W can be stored for a maximum of 11 days at 4°C. This allows for up to 8 h additional storage at 23°C. Under these conditions, more than 90.27% of the initial concentration will remain, with 95% confidence.

Because solutions of pantoprazole diluted in NS degraded at a slower rate, a maximum stability of 20 days was calculated for concentrations between 0.16 mg and 0.80 mg/mL. Under these conditions, if admixtures in NS are stored for 20 days at 4°C and then stored at room temperature for additional 6 h, more than 90.33% of the initial concentration will remain, with 95% confidence.

For the treatment of upper gastrointestinal bleeding, some institutions prepare pantoprazole for injection as a single

admixture (typically 200 mg in 250 mL NS or 0.8 mg/mL) and infuse it continuously over a 24-h period. If an additional 4 h of exposure at room temperature is allowed to account for preparation and delivery time, the results of the current study indicate that pantoprazole for injection at a concentration of 0.8 mg/mL in NS can be stored for up to 10 days at 4°C plus an additional 28 h at room temperature. Under these conditions more than 90.52% of the initial concentration will remain, with 95% confidence.

An overall summary of these recommended storage conditions is provided in Table 2.

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### Acknowledgements

This study was funded by an unrestricted educational grant from Nycomed Canada Inc.