DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

**TRANSMITTED VIA FACSIMILE** NOV 28 2000

Mary Alice Dankulich
Associate Director
Worldwide Regulatory Affairs
Wyeth-Ayerst Research
P.O. Box 8299
Philadelphia, PA 19101-8299

Re: **NDA [ ]/20-987**
**Protonix I.V. (pantoprazole sodium) for Injection**
**Protonix (pantoprazole sodium) Delayed-Release Tablets**
**MACMIS ID #9542**

Dear Ms. Dankulich:

This letter concerns violative promotional activities by Wyeth-Ayerst Laboratories (WA) for its unapproved product, Protonix I.V., and its approved product, Protonix Tablets. As part of its monitoring and surveillance program, the Division of Drug Marketing, Advertising, and Communications (DDMAC) has determined that WA promoted Protonix I.V. as safe or effective prior to the product's approval and promoted Protonix Tablets for unapproved uses. This promotion is in violation of the Federal Food, Drug, and Cosmetic Act and applicable regulations. Specifically, we object to the following:

**Pre-approval Promotion Panel**

WA promoted Protonix I.V. prior to approval in the commercial exhibit area at the October American College of Gastroenterology (ACG) Annual Scientific Meeting in New York City. In the commercial exhibit area, WA displayed a lighted panel with the name "PROTONIX I.V. (pantoprazole sodium for injection)." The panel included a picture of a stomach in the "O" of "Protonix" with an I.V. bag background and a banner that stated "approval expected soon." This panel is violative because it makes a conclusion about the safety or efficacy of the product.

Mary Ann Dankulich
Wyeth Ayerst Research
NDA [ ]20-987

In addition, WA failed to reveal facts that are material in light of the representation made about Protonix I.V. The product has not been approved by the FDA due to [

]

**Other Violative Promotional Activities and Materials in the Commercial Exhibit Area**

WA disseminated materials in the commercial exhibit area for Protonix I.V. prior to approval. These materials included three company talk papers that compared Protonix I.V. with Protonix Tablets, discussed the use of Protonix I.V. for upper gastrointestinal (UGI) bleed, and discussed the use of Protonix I.V. and tablets in the treatment of Zollinger-Ellison Syndrome (ZES). These materials made conclusions about the safety or efficacy of Protonix I.V. prior to approval and promoted unapproved uses for the tablet formulation. Further, WA failed to reveal facts that are material in light of the representations made about Protonix I.V. WA failed to provide information about [ ]

**Other Pre-Approval Promotion**

WA is also promoting Protonix I.V. prior to approval by disseminating a reprint entitled "Pantoprazole: A new benzimidazole proton pump inhibitor for oral and administration." This reprint makes conclusions about the safety or efficacy of Protonix I.V. for a wide-range of non-approved diseases such as eradication of *Helicobacter pylori*, gastric and duodenal ulcers, and ZES. The reprint also promotes Protonix Tablets for unapproved uses.

**Requested Action**

DDMAC requests that WA immediately cease the violative promotion as explained in this letter. WA should submit a written response to DDMAC, on or before December 12, 2000, describing its intent and plans to comply with our request. In its response to DDMAC, WA should include a list of all promotional materials that were discontinued, and the discontinuation date.

WA should direct its response to Patricia Staub by facsimile at (301) 594-6759, or by written communication at the Division of Drug Marketing, Advertising, and Communications, HFD-42; Room 17B-20; 5600 Fishers Lane; Rockville, MD 20857.

In all future correspondence regarding this matter, please refer to MACMIS #9542 and NDA [ ]/20-987.

Sincerely,

/S/

Patricia Kuker Staub, R.Ph, J.D.
Regulatory Review Officer
Division of Drug Marketing,
Advertising, and Communications

WYETH-AYERST PHARMACEUTICALS
Division of American Home Products Corporation
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**A comparison of Protonix® IV (sterile pantoprazole sodium, Wyeth Laboratories) and Protonix® Tablets (pantoprazole sodium, Wyeth Laboratories).**

Protonix is indicated for the short-term treatment (up to 8 weeks) in the healing and symptomatic relief of erosive esophagitis.[1] For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of Protonix may be considered. Protonix IV will be indicated for the short-term treatment (7 to 10 days) of gastroesophageal reflux disease (GERD) in patients unable to take the oral formulation.[2] Summarized below are clinical trial publications which compare the pharmacokinetics, potency and efficacy of the oral versus the IV formulations.[3-7]

*Pharmacokinetics*

Pue et al conducted a study to compare the pharmacokinetic profiles of Protonix IV and tablets.[3] Twelve healthy male subjects, ages 19 to 29 years, received Protonix 40 mg as a 15-minute intravenous infusion and oral tablets in a randomized cross-over study. All subjects fasted overnight and for 5 hours post-dose. The results of this study showed that following a single IV infusion of Protonix 40 mg, maximum plasma concentrations ranged between 3.21 and 7.05 mcg/mL; by twelve hours after the dose, serum pantoprazole levels were virtually non-existent. The mean values for other pharmacokinetic parameters were as follows: $t_{1/2}$, 1.9 hours; volume of distribution, 0.17 L/kg; and estimated clearance, 0.129 L/h•kg. Following oral administration, onset of absorption was variable. Maximum plasma concentrations were reached within 2 to 4 hours post-dose, with a mean value of 2.09 mcg/mL. The half-life of pantoprazole after oral administration was equivalent to the intravenous formulation. The bioavailability after oral administration of Protonix was 77% in this study.

*Gastric Acid Inhibition*

The antisecretory effect of oral and intravenous Protonix 40 mg were compared in 20 healthy volunteers to determine the equivalent dose.[4] Subjects were randomized to receive daily doses of 40 mg of oral or intravenous Protonix for 5 days with a crossover after a 2-3 week wash-out period. Intravenous administration resulted in a slightly faster onset of action. The median pH profiles were similar with both routes of administration. Mean baseline 24-hour pH was 1.4. After 5 days of treatment with Protonix, mean pH values were 3.3 and 3.1, the percent of time pH was ≥3 was 57% and 51%, and the percent of time pH was ≥4 was 42% and 38% after intravenous and oral administration, respectively. Both formulations reduced pH fluctuations after meals and at night. The authors concluded that Protonix is equipotent in antisecretory activity when administered by either the intravenous or oral route.

Paul et al conducted a study to assess the ability of Protonix IV to maintain gastric acid suppression in patients with GERD achieved with Protonix tablets therapy.[5] Sixty-five GERD patients with a history of erosive esophagitis were randomized to receive either 20 or 40 mg Protonix tablets once a day for 10 days. Patients were then switched to either a matching dose of Protonix IV or placebo IV for 7 days. The maximum pentagastrin-stimulated acid output (MAO)

in the 40 mg group at the end of oral therapy was 6.49 mEq/h and at the end of IV therapy was 6.62 mEq/h. The 20 mg group had MAO values of 14.50 mEq/h and 12.83 mEq/h after oral and IV therapy, respectively. Patients receiving placebo IV showed a loss of acid control after 48 hours, with a significant increase from 14.24 mEq/h to 29.2 mEq/h by day 7 ($p<0.05$). The authors concluded that acid output is reduced with both Protonix 40 mg IV and tablets. Protonix IV effectively suppressed the increase in AO when oral therapy is discontinued and maintained acid suppression when patients were switched from the tablet formulation.

*Healing and Symptom Relief of Erosive Esophagitis*

Fumagalli et al conducted a double-blind trial to compare the symptom relief and healing rates of reflux esophagitis of Protonix IV and tablet formulations.[6] Forty-five patients with GERD grade II/III (Savary/Miller) were randomized to receive Protonix 40 mg IV or tablets once a day for 5 days, followed by oral administration of Protonix 40 mg for a total of eight weeks. Within 3 days, patient-reported symptoms (acid eructation, heartburn, and pain on swallowing) were markedly decreased in both the IV and oral groups. At week 4, complete resolution of acid eructation, heartburn, and pain on swallowing were reported in 100%, 95%, and 100% of the patients in the IV/PO group, and 95%, 90% and 100% of patients in the PO group, respectively. Esophagitis healing was reported at 8 weeks in 87% of the IV/PO group and 86% of the PO group. No serious adverse events occurred in either group. The authors concluded that sequential therapy with Protonix IV and tablets has a similar efficacy and safety profile as therapy with Protonix tablets alone for the healing and symptom relief of reflux esophagitis in stage II/III patients.

The enclosed information is supplied as a professional courtesy in response to your inquiry. It is intended to provide pertinent data to assist you in forming your own conclusions and making decisions. This information is not intended to advocate any indication, dosage, or other claim that is not covered in the enclosed package insert.

AJQ/PRO013/app 3-17-00/rr 4-27-00 MBM

References:

1. Protonix - current prescribing information.

2. Protonix IV – draft prescribing information.

3. Pue, MA et al. Pharmacokinetics of pantoprazole following single intravenous and oral administration to healthy male subjects. *Eur J Clin Pharmacol* 44(6):575-578, 1993.

4. Hartmann, M et al. Equipotent inhibition of gastric acid secretion by equal doses of oral or intravenous pantoprazole. *Aliment Pharmacol Ther* 12(10):1027-1032, 1998.

5. Paul, J et al Pharmacodynamic equivalence of oral & IV pantoprazole in GERD patients. *Am J Gastroenterol* 93(9):1622, Abs: 53, 1998.

6. Fumagalli, I et al. Comparison of intravenous with oral pantoprazole in symptom relief and healing of erosive esophagitis. *Digestion* 59(Suppl. 3):610, Abs: B4233, 1998.

***The information you requested is provided as a service of Global Product Information, Wyeth-Ayerst Pharmaceuticals. For additional medical information regarding Protonix, please contact us at 1-800-934-5556.***

WYETH-AYERST PHARMACEUTICALS

P.O. Box 8299, Philadelphia, PA 19101-8299 • (610) 902-1200 Division of American Home Products Corporation

**The use of Protonix® (pantoprazole sodium, Wyeth Laboratories) to treat patients with Zollinger-Ellison syndrome (ZES).**

Protonix is not indicated for the treatment of ZES. However, several studies have been conducted to evaluate its efficacy in controlling acid output (AO) in these patients.[1-3] These studies have been summarized below for your review.

*Intravenous*

Two studies were conducted to evaluate the control of acid hypersecretion with intravenous Protonix.[1,2] All patients had been controlled with an oral proton-pump inhibitor (PPI) therapy prior to entering the study. Control of AO was defined as <10 mEq/h of acid production (<5 mEq/h in patients with prior gastric acid reducing surgery).

Ten ZES patients (age range 32 to 64 years) were entered into the first study.[1] Patients received Protonix 80 to 120 mg every 8 to 12 hours as a 15 minute infusion for 7 days. Mean prestudy basal AO was 37.8 ± 6.9 mEq/h (range 15.2 to 84.5 mEq/h). After administration of an initial dose of 80 mg Protonix, AO was controlled within the first hour for all patients. Mean AO following the initial dose was 3.6 ± 1.1 mEq/h at 24 hours and 2.6±2.8 mEq/h at 48 hours. Seven of the 10 patients were controlled on a dose of 80 mg every 12 hours for up to 7 days. Of the patients that were not controlled at this dose, one was subsequently controlled with 120 mg every 12 hours. The other 2 patients were controlled with a dose of 80 mg every 8 hours. The investigators concluded that Protonix IV was effective in controlling AO in ZES patients unable to take oral medications.

The second study investigated replacing oral PPI therapy with IV Protonix in 14 ZES patients (age range 38 to 67 years).[2] All patients had been effectively controlled with oral PPI therapy prior to entering the study. Patients received a 15 minute infusion of Protonix 80 mg twice daily for 7 days. The dose could be titrated up to 240 mg/24 h in patients where AO was not controlled. Mean AO on oral therapy was 0.55 mEq/h. Thirteen of the 14 patients were controlled on the 80 mg BID dose with AO not significantly different from baseline. One patient was titrated to 120 mg BID after day 2. AO was 11.3 mEq/h on day 2 and 12.7 mEq/h on day 7 in this patient. Control of AO established with oral PPIs was maintained in 93% of patients with Protonix IV 80 mg BID.

Both studies showed mean AO values of <1 mEq/h two hours after administration of pantoprazole.[3]

*Oral*

The safety and efficacy of oral Protonix was evaluated in 10 patients with ZES over a 3 year period.[5] The mean basal acid output (BAO) was 25.9 mmol/h (range 0.5-97.8 mmol/h). The goal of therapy was to reduce AO to <10mmol/h (<5 mmol/h in patients with previous acid

reducing operations). A daily dose of 40 mg Protonix achieved the target AO in the 6 patients with a BAO of <20 mmol/h. Three patients had a high BAO (range 36.5 to 97.8 mmol/h) with no evidence of mucosal disease. These patients were asymptomatic on 120 mg Protonix, despite AO >10 mmol/h (18.0, 18.0 and 29.1 mmol/h). Increasing the dose to 160 mg divided in two daily doses reduced AO further (12.1, 10.3 and 3.7 mmol, respectively). The final patient had a BAO of 43.5 mmol/h and was controlled initially on 80 mg Protonix. This dose was increased to 160 mg after 12 months of treatment to maintain control of AO. Treatment with Protonix was well-tolerated.

The enclosed information is supplied as a professional courtesy in response to your inquiry. It is intended to provide pertinent data to assist you in forming your own conclusions and making decisions. This information is not intended to advocate any indication, dosage, or other claim that is not covered in the enclosed package insert.

AJQ/PRO009/app 6-15-99

References:

1. Metz, DC et al. Intravenous (IV) pantoprazole (PANTO) rapidly and effectively controls acid output (AO) in patients with Zollinger-Ellison syndrome (ZES). *Gastroenterology* 114 (4, Suppl.):A226, 1998.

2. Metz, DC et al. Zollinger-Ellison syndrome patients can replace oral proton pump inhibitors with intravenous pantoprazole without losing control of acid output. *Gastroenterology* 116(4):A252:Abs G1100, 1999.

3. Data on file, Wyeth-Ayerst.

4. Radebold, K et al. Preliminary results of the proton-pump inhibitor pantoprazole in patients with Zollinger-Ellison syndrome. *Gastroenterology* 112(4, Suppl.):A37, 1997

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WYETH-AYERST PHARMACEUTICALS

P.O. Box 8299, Philadelphia, PA 19101-8299 • (610) 902-1200 Division of American Home Products Corporation

**The use of Protonix® IV (pantoprazole sodium, Wyeth Laboratories) as supportive therapy for patients with upper gastrointestinal (UGI) bleeding.**

When approved, Protonix IV will be indicated for the short-term treatment (7 to 10 days) of gastroesophageal reflux disease (GERD) in patients who are unable to continue taking the oral formulation.[1] Protonix IV will be approved as a 15-minute infusion. Therefore, we can not recommend the use of Protonix for supportive use in UGI bleeding or as a rapid bolus injection. However, a search of published medical literature revealed several studies that discuss the use of Protonix IV and omeprazole IV in treating this patient population.[2] These articles are summarized below for your review.

*pH Studies*

Blood coagulation and platelet aggregation require pH values >5.9.[2] Raising the pH to a value >5.9 will optimize the conditions for hemostasis in UGI bleeding. The ideal pH for hemostasis is 7.4.

The optimal dosing regimen of Protonix IV to obtain achlorhydria as a supportive measure in patients with UGI bleeding was determined by Brunner et al.[2] The results of four administration schedules were compared, as measured by median percent time above various pH values. All volunteers entered the study with an empty stomach and continued fasting until completion of the treatment period. Regimens studied in this pilot trial included: 1) 80 mg bolus* followed by Q8H 40 mg bolus injections for 48 hours (n=8); 2) 40 mg bolus followed by an 4 mg/hr infusion versus placebo (n=6); 3) 80 mg bolus followed by an 8 mg/hr infusion for 24 hours versus a 48 mg/hr infusion for 2 hours followed by an 8 mg/hr infusion for 22 hours. The 80 mg IV bolus followed by an 8 mg/hr infusion regimen was the most effective with respect to raising pH, showing the greatest median percent time above pH 3, 4, 5, and 6 (99%, 99%, 94%, and 84%, respectively). The desired pH of 7 was achieved within 20 minutes when initial dosing used a 2-minute bolus infusion. Spreading the bolus over time delayed the maximum pH effect by 12 hours. Treatment was well-tolerated with no adverse events considered clinically significant or drug-related. The authors concluded that an 80 mg bolus followed by an 8 mg/hr infusion was the best regimen in situations where achlorhydria is desired rapidly.
**All bolus infusions were administered over 2 minutes.*

*Prevention of Rebleeding pH Studies*

The use of Protonix IV was evaluated in 20 patients of which 17 patients with bleeding peptic ulcers (Forrest Ia, Ib, or IIa) were considered evaluable.[3] Two hours after endoscopic hemostasis, Protonix was administered as an 80 mg bolus followed by a continuous infusion of 8 mg/hr for 72 hours. From days 4 to 7, Protonix was administered in a dose of 40 mg bolus Q12H. In the 14 patients with 48 hour intragastric pH data, the median pH was 6.3 with

Protonix administration. The median percent time above pH 4, 5, and 6 for the same time period was 97.5%, 90.5% and 64.3%, respectively. The median percent time above pH 4, 5, and 6 for the time period of 24 to 48 hours were 99.6%, 91.1%, and 58.4%, respectively. Four patients experienced thrombophlebitis at the injection site, but causality was not assessed.

van Rensburg completed a second study with the same design, using a Protonix dose of 80 mg bolus followed by a 6 mg/hr continuous infusion for 72 hours.[4] From days 4 to 7, Protonix was given as a single daily bolus of 40 mg. In the 17 patients with 48 hour intragastric pH data, the median pH was 5.9 with Protonix administration. The median percent time above pH 4, 5, and 6 for the same time period was 91%, 77% and 47%, respectively. The median percent time above pH 4, 5, and 6 for the time period of 24 to 48 hours was 98%, 81%, and 61%, respectively. The treatment was well-tolerated in all patients. The author concluded that although the 6 mg/hr infusion raised intragastric pH effectively, compared to the 8 mg/hr infusion, the interindividual variability was higher. Therefore, the 8 mg/hr continuous infusion dose would be preferred in this patient population.

*Prevention of Rebleeding Clinical Outcomes Studies*

Two different doses of Protonix IV were studied in 168 inpatients for the prevention of peptic ulcer bleeding (Forrest Ia, Ib, and IIa).[5] One hour after endoscopic hemostasis, patients were randomized to receive for 3 days either Protonix IV 40 mg once daily (low dose, n=82) or Protonix IV 40 mg initially followed by an 8 mg/hr continuous infusion (high dose, n=86). Rebleeding rates after 72 hours were 12% (9/74) for the low dose and 13% (10/76) for the high dose per-protocol populations. *Helicobacter pylori* status had no apparent effect on rebleeding. Both dosage regimens resulted in similar requirements for blood transfusions. After 14 days, mortality rates were 2.5% (2/78) and 2.4% (2/80) for the low and high dose groups, respectively. Adverse events occurred more frequently in the low dose group. Overall, both dosage regimens were similar in efficacy for the prevention of peptic ulcer rebleeding.

A similar study by Fried et al compared the efficacy of Protonix IV with ranitidine IV over 2 days for the prevention of peptic ulcer rebleeding.[6] One hour after endoscopic hemostasis, patients were randomized to receive Protonix IV 40 mg initially followed by a continuous infusion of 8 mg/hr (n=66) or intravenous ranitidine 50 mg followed by a continuous infusion of 12.5 mg/hr (n=67) for 2 days. The rebleeding rates after 48 hours were 10% in both treatment groups. The author noted that a tendency for lower rebleeding rates was seen in the Protonix per-protocol population. The mortality rate after 10 days was 1.5% for both groups.

In a double-blind study in Hong Kong, Lau et al evaluated the effect of IV omeprazole on 240 recurrent bleeding patients after endoscopic treatment with epinephrine and thermocoagulation of a bleeding peptic ulcer.[7] Patients were randomly assigned to receive either IV omeprazole (80 mg bolus dose followed by 8 mg/hour infusion) or placebo for 72 hours then 20 mg of oral omeprazole daily for 8 weeks. Recurrent bleeding within 30 days of endoscopy occurred in 8 patients (6.7%) in the omeprazole group and 27 patients (22.5%) in the placebo group ($p< 0.001$). Most of the bleeding recurred within the first 72 hours (5 patients in the omeprazole group and 24 in the placebo group, $P <0.001$). Surgery was performed on 3 patients in the omeprazole group and 9 patients in the placebo group ($P=0.14$). Death within 30 days of

endoscopy occurred in 5 patients in the omeprazole group and 12 patients in the placebo group (P=0.13). The number of units of blood transfused and the duration of hospitalization was noted to be significantly less for the omeprazole group. The authors concluded that a high-dose infusion of omeprazole reduced the rate of recurrent bleeding, decreased the need for endoscopic re-treatment and blood transfusions, and shortened the length of hospitalization.

An editorial by Eric D. Libby, M.D. on the above article, suggests that clinical trials with omeprazole have not consistently shown benefits to patients with acute GI bleeding, in part due to differences in patient population, dosing, and design.[8] Dr. Libby does, however, mention that a pH of 6.0 or more is required for platelet aggregation and a pH below 5.0 may be associated with lysis of clots. He also mentions that continuous infusions of H2RAs initially raise intragastric pH, but pH usually falls to levels between 3.0 and 5.0 within 24 hours. Further studies investigating the use of PPIs are needed to establish their role in the treatment of UGI bleeding.

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KW/PRO018/app 9-12-00

References:


1. Protonix IV® - draft prescribing information

2. Brunner, G et al. Optimizing the intragastric pH as a supportive therapy in upper GI bleeding. *Yale J Biol Med* 69:225-231, 1996.

3. van Rensburg, CJ et al. Intragastric pH in patients with bleeding peptic ulceration during pantoprazole infusion of 8 mg/hr. *Gut* 41(3, Suppl.):A98, Abstract P079, 1997.

4. van Rensburg, CJ et al. Intragastric pH during pantoprazole infusion of 6 mg/hour in patients with bleeding peptic ulceration. *Gastroenterology* 116(4):A344-A345, Abstract G1505, 1999.

5. Schönekas, H et al. Comparison of two doses of intravenous pantoprazole in peptic ulcer bleeding. *Can J Gastroenterol* 13(Suppl. B):154B; Abstract 102, 1999.

6. Fried, R et al. Comparison of intravenous pantoprazole with intravenous ranitidine in peptic ulcer bleeding. *Gastroenterology* 116(4):A165, Abstract G0716, 1999.

7. Lau, JY et al. Effect of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. *The N Eng J of Med* 343(5):310-316.

8. Libby, E.D. Editorial. *The N Eng J of Med* 343(5):358-359.

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