

May 18, 2005

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
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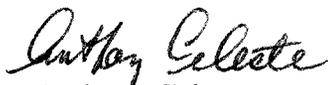
RE: Citizen Petition

Dear Sir or Madam,

Please find enclosed two copies of the petition submitted by Sun Pharmaceutical Industries, Ltd. requesting FDA make a determination that Pantoprazole sodium injection 40 mg per vial is suitable for submission as an Abbreviated New Drug Application.

If you have any questions or require additional information, please let us know.

Sincerely,


Anthony Celeste
Senior, Vice President

Enclosure

2005 P-0196

Sun Pharma Advanced Research Centre (SPARC)
Tandalja, Vadodara - 390 020, INDIA.
Tel. : 91- 265 - 2350756 / 0775 / 2352041 / 2420.
Fax : 91- 265 - 2354897



CITIZEN PETITION

The undersigned submits this petition under section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act and 21 CFR § 314.93 and 21 CFR §10.30 to request the Commissioner of Food and Drugs to make a determination that the discontinued formulation of PROTONIX® I. V. for injection containing pantoprazole sodium (equivalent to 40 mg pantoprazole) in a vial requiring storage of vials at 2°C – 8°C (36°F – 46°F), is suitable for submission as an Abbreviated New Drug Application (ANDA).

A. Action Requested

The petitioner requests the Commissioner of Food and Drugs to make a determination that the discontinued formulations of Protonix® I. V. for injection containing pantoprazole sodium (equivalent to 40 mg pantoprazole) per vial requiring storage of vials at 2°C – 8°C (36°F – 46°F), was not discontinued for safety and efficacy reasons. The petitioner particularly requests the FDA to make a determination that the proposed generic product referring to the originally approved formulation (now discontinued) would not render the product less safe or effective than the currently marketed innovator's product. The petitioner further requests the FDA to accept Abbreviated New Drug Application (ANDA) for Pantoprazole for Injection (hereinafter referred to as "proposed generic product") containing pantoprazole sodium equivalent to 40 mg pantoprazole/vial requiring storage of vials at 2°C – 8°C (36°F – 46°F) without an in-line filter for the reasons discussed herein below.

B. Statement of Grounds

I. Background:

The active ingredient in Protonix® I. V. for injection is pantoprazole sodium, a proton pump inhibitor (PPI) that inhibits the gastric acid secretion. Protonix® I.V. for injection is indicated for short-term treatment (7 to 10 days) of patients having gastroesophageal reflux disease (GERD) with a history of erosive esophagitis, as an alternative to oral therapy in patients who are unable to continue taking PROTONIX Delayed-Release Tablets.

Originally approved formulation ("Old Formula I"): Protonix® I. V. for injection containing pantoprazole sodium (equivalent to 40 mg pantoprazole per vial) by Wyeth Pharmaceuticals Inc ("Wyeth") was first approved on March 22, 2001 under NDA 020988. The product was supplied as a freeze-dried powder in a clear glass vial fitted with a rubber stopper and crimp seal containing pantoprazole sodium equivalent to 40 mg pantoprazole. It was recommended that each vial be reconstituted with 10 ml of 0.9 % sodium chloride injection USP, and further diluted with 100 ml of 5 % dextrose injection USP, 0.9 % sodium chloride injection USP or lactated Ringer's injection USP to a final concentration of approximately 0.4 mg/ml and be administered through a dedicated line, using the in-line filter provided. The discontinued formulation required storage of vials at 2°C – 8°C (36°F – 46°F) and protection from light. A copy of the first approved labeling is provided herewith as Exhibit I.

The discontinued Protonix® I.V. formulation has been used clinically for seven years in more than five million patients worldwide.³

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Revised formulation ("Old Formula II"): Subsequently, Wyeth reformulated its Protonix[®] I. V. for injection with its supplemental application no. S024 (attached herewith as Exhibit II). The product was supplied as a freeze-dried powder in a clear glass vial fitted with a rubber stopper and crimp seal containing pantoprazole sodium equivalent to 40 mg pantoprazole, edetate disodium (1 mg) and sodium hydroxide to adjust pH. It was recommended that each vial be reconstituted with 10 ml of 0.9 % sodium chloride injection USP, and further diluted with 100 ml of 5 % dextrose injection USP, 0.9 % sodium chloride injection USP or lactated Ringer's injection USP to a final concentration of approximately 0.4 mg/ml. This revised formulation eliminates use of in-line filter, however, it requires storage of vials at 2°C – 8°C (36°F – 46°F) and protection from light.

New formulation: Wyeth for the second time reformulated Protonix[®] I. V. (pantoprazole sodium) for Injection with supplemental application no. S027. The product is supplied as a freeze-dried powder in a clear glass vial containing pantoprazole sodium (equivalent to 40 mg pantoprazole), edetate disodium (1 mg) and sodium hydroxide to adjust pH. The new formulation does not require storage at 2°C – 8°C and can be stored at room temperature and eliminates the need for an in-line filter. For the new formulation also, it was recommended that each vial be reconstituted with 10 ml of 0.9 % sodium chloride injection USP, and further diluted with 100 ml of 5 % dextrose injection USP, 0.9 % sodium chloride injection USP or lactated Ringer's injection USP to a final concentration of approximately 0.4 mg/ml. A copy of the new formulation is attached herewith as Exhibit III.

II. Referencing discontinued labeling:

It is known from the Code of Federal Regulations that when an ANDA makes a reference to a discontinued label of a drug, FDA may still approve the ANDA upon determination that the formulation was not withdrawn for reasons of safety or effectiveness (21 U.S.C. Section 355 (j)(6) and 21 CFR §§ 314.122 and 314.161).¹ Similarly FDA is also authorized to approve an ANDA that omits in its labeling an indication or other aspects for the listed drug.⁵ In this circumstance, omission from the NDA's labeling of protected aspects is allowed if the omission does not render the generic drug product less safe or effective than the listed drug. (21 CFR §314.127(a)(7)).²

The petitioner is not aware of any documentation which establish that the original formulation ("old formula I") of the Protonix[®] for injection was discontinued for safety or efficacy reasons. The discontinued Protonix[®] I.V. formulation has been used clinically for seven years in more than five million patients worldwide.² In fact news dated Nov. 16, 2004 published on Wyeth's website clearly indicated that room temperature storage of Protonix[®] I. V. for injection provides a substantial improvement with respect to how PROTONIX I.V. is stocked in hospital pharmacies and patient care areas and that filterless administration can contribute to ease of use when administering PROTONIX I.V. to hospitalized patients.³

III. Proposed generic product:

The proposed product is identical to the discontinued formulation of Protonix[®] I. V. for Injection and is supplied as a freeze-dried powder in a clear glass vial containing pantoprazole sodium equivalent to 40

¹ Although the regulations are consistent with relief sought, this citizen petition is submitted pursuant to section 505(j)(2)(C) of the Federal Food Drug, and Cosmetic Act ("The FDC Act") and 21 CFR § 314.93.

² 21 CFR § 314.127 (a)(7): Information submitted in the ANDA is insufficient to show that the labeling proposed for the drug is the same as the labeling approved for the listed drug referred to in the ANDA except for changes required because of differences approved in a petition under § 314.93 or because the drug product and the reference listed drug are produced or distributed by different manufacturers or because aspects of the listed drug's labeling are protected by patent, or by exclusivity, and such differences do not render the proposed drug product less safe or effective than the listed drug for all remaining, nonprotected conditions of use.

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mg of pantoprazole which require storage of the product at 2°C – 8°C. The formula of proposed product, which is subject of this petition, is provided in the following Table I.

Table I

Ingredients	Quantity per 10 ml vial
Pantoprazole sodium (equivalent to pantoprazole base)	40 mg
Water for injection	Quantity sufficient

Other details of petitioner's product are provided in the label attached as Exhibit IV. The petitioner's product labeling does not recommend an in-line filter while intravenously administering pantoprazole injection to the patient.

IV. Rationale for the proposed product:

The first approved Protonix® I. V. for injection required administering the reconstituted injection intravenously through a dedicated line using in-line filter. The use of filter was recommended to remove the precipitates that may form when the reconstituted drug product is mixed with I.V. solution. It is highly recommended that parenteral formulation should be essentially free from particulate matter prior to administration. The US Pharmacopoeia (USP) specifies a limit for the presence of particulate matter in injections. As per the USP 26 the average limit of particles in small-volume injections for particles of size $\geq 10 \mu\text{m}$ is 6000 particles per vial and for particles of size $\geq 25 \mu\text{m}$ is 600 particles per vial. The average number of particles present in the proposed generic product was analyzed by the "Light Obscuration Particle Count Test" prescribed in the USP 26. The number of particles of the specified particle size(s) in the proposed generic product was tested before admixing with diluents after 3 months and 6 months of storage at 2°C to 8°C. The number of particles of the specified particle size(s) was also tested for the proposed product after reconstitution with saline after 6 months of storage at 2°C to 8°C. The analytical test procedure and the results of the particulate matter in the proposed product are provided in the attached Exhibit V.

It is evident from the results specified in Table II (Exhibit V) that the number of particles of the specified particle size(s) is much lower than the prescribed limit even after 3 months of storage at 2°C to 8°C and also the results specified in Table III (Exhibit V) indicate that the number of particles are lower than the limit prescribed in the USP 26.

Since the proposed product meets the requirement for the presence of particulate matter as prescribed in the USP 26, the petitioner respectfully submits that the FDA accept the petitioner's Abbreviated New Drug Application (ANDA) for pantoprazole for injection (containing pantoprazole sodium equivalent to 40 mg pantoprazole/vial requiring storage of vials at 2°C – 8°C (36°F – 46°F)) without an in-line filter. However, on review if FDA is of the opinion that it is essential to provide in-line filter with the proposed product, the petitioner agrees to provide the same.

³ DG News : "FDA Approves New Formulation for Proton Pump Inhibitor Protonix (Pantoprazole) I.V. - New Formulation Provides Filterless Administration -MADISON, NJ -- April 13, 2004.

Wyeth : News & Announcements titled "Wyeth Announces FDA Approval of Room Temperature Shipping and Storage for Protonix I.V. (pantoprazole sodium) for Injection" dated November 15, 2004.

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V. Conclusion

For all the reasons stated above in this statement grounds, the petitioner seeks FDA to make a determination that the discontinued formulation of protonix was not voluntarily withdrawn by Wyeth for reasons of safety or effectiveness and that the use of that labeling by the proposed product would not render the proposed product less safe or effective and would be therapeutically equivalent to the currently marketed product, protonix (pantoprazole sodium) for injection. The petitioner also seeks from the FDA a waiver to the requirement of providing an in-line filter with its proposed product.

Accordingly, this petition seeks a determination that the discontinued formulation of protonix[®] I.V. for injection, is suitable for submission as an Abbreviated New Drug Application (ANDA).

C. Environmental Impact

This petition is entitled to a categorical exclusion under 21 CFR §§ 25.30 and 25.31

D. Economic Report

The petitioner agrees to provide an economic analysis if requested by the agency.

E. Certification

The undersigned certifies that, 'to the best knowledge and belief of the undersigned, this petition includes all information and review upon which the petitioner relies, and that it includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,

A handwritten signature in black ink, appearing to read "Abhay Muthal", is written over a horizontal dashed line.

Dr. Abhay Muthal
Dy. General Manager , Regulatory Affairs.