

**Memorandum**

Date:           MAY 15 2006          

From: Consumer Safety Officer, Division of Dietary Supplement Programs , Office of  
Nutritional Products, Labeling and Dietary Supplements, HFS-810

Subject: 75-Day Premarket Notification of New Dietary Ingredients

To: Dockets Management Branch, HFA-305

Subject of the Notification: Benfotiamine/Alpha-Lipoic Acid Combination

Firm: The Pryde Company

Date Received by FDA:

90-Day Date: May 5, 2006

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and  
Cosmetic Act, the attached 75-day premarket notification and related correspondence for the  
aforementioned substance should be placed on public display in docket number 95S-0316 as  
soon possible since it is past the 90-day date. Thank you for your assistance.

          Victoria Lutwak          

19955-0316

RPT389



APR 13 2006

Eric J. Scopp  
V.P. Operations  
The Pryde Company  
258 S.E. 6th Ave, Ste. 12  
Delray Beach, Florida 33483

Dear Mr. Scopp:

This is to inform you that the notification, dated January 16, 2006, you submitted pursuant to 21 U.S.C. 350b(a)(2)(section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)) was filed by the Food and Drug Administration (FDA) on February 7, 2006. The notification concerns the substance called "Benfotiamine/Alpha-Lipoic Acid Combination" which you assert is a new dietary ingredient.

According to your notification, you plan to market two strengths of "Benfotiamine/Alpha-Lipoic Acid Combination." "The ordinary conditions of use are: one 225 mg pill consisting of 75 mg of Benfotiamine and 150 mg of Alpha-Lipoic Acid two times a day by mouth or one 450 mg pill consisting of 150 mg of Benfotiamine and 300mg of Alpha-Lipoic Acid two times a day by mouth for a total of 300 mg of Benfotiamine and 600 mg of Alpha-Lipoic Acid per day by mouth."

Under 21 U.S.C. 350b(a), the manufacturer or distributor of a dietary supplement containing a new dietary ingredient that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered must submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under 21 U.S.C. 350b(a)(2), there must be a history of use or other evidence of safety establishing that the new dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is considered to be adulterated under 21 U.S.C. 342(f)(1)(B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

Your notification concerning "Benfotiamine" does not comply with the requirement of 21 CFR 190.6 and is incomplete. For example, your notice did not provide information on the composition or describe the manufacturing process of the dietary supplement containing a new dietary ingredient. Without this information the identity of you new dietary ingredient is unclear. In addition, without inclusion of a summary of safety, it is unclear how the substances discussed in the referenced studies are relevant to evaluating the safe use of the dietary supplement containing a new dietary ingredient.

Furthermore, it is not evident whether "Benfotiamine/Alpha-Lipoic Acid Combination" which is the subject of your notification is a dietary ingredient within the meaning of 21 U.S.C. 321(ff)(1) that may be lawfully used in dietary supplements. The term "dietary supplement" is defined in 21 U.S.C. 321(ff). A dietary supplement means, among other things, a "product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:

- (A) a vitamin;
- (B) a mineral;
- (C) an herb or other botanical;
- (D) an amino acid;
- (E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or
- (F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E)."

Based on the information in your submission, it is unclear that "Benfotiamine/Alpha-Lipoic Acid Combination" is a "dietary ingredient" within the meaning of 21 U.S.C. 321(ff)(1).

FDA is unable to determine whether the scientific studies cited in your notice provide an adequate basis for a conclusion that the dietary supplement will reasonably be expected to be safe because the information contained in your notice is incomplete. If you market your product without submitting a notification that meets the requirements of 21 CFR 190.6 (<http://www.cfsan.fda.gov/~lrd/cfr190-6.html>), or market your product less than 75 days after submitting such a notification, your product is considered adulterated under 21 U.S.C. 342(f)(1)(B) as a dietary supplement that contains a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury. Introduction of such a product into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v).

Your notification will be kept confidential for 90 days after the filing date of February 7, 2006. After the 90-day date, the notification will be placed on public display at FDA's Docket Management Branch in docket number 95S-0316. Prior to that date, you may wish to identify in writing specifically what information you believe is proprietary, trade secret or otherwise confidential for FDA's consideration.

If you have any questions concerning this matter please contact Linda Pellicore, Ph.D.,  
at (301) 436-2375.

Sincerely yours,



**Susan J. Walker, M.D.**  
**Director**  
**Division of Dietary Supplement Programs**  
**Office of Nutritional Products, Labeling**  
**and Dietary Supplements**  
**Center for Food Safety and Applied Nutrition**

# THE PRYDE COMPANY

Corp: 258 S.E. 6th Ave. Ste.12, Delray Beach, FL 33483  
Sales: 21 N. Brown Ave. Orlando, FL 32801  
407.897.0950 • Toll Free: 866.PRYDE10 • Fax: 407.228.4936

January 16, 2006

**CERTIFIED MAIL - RETURN RECEIPT REQUESTED  
TRADE SECRET - CONFIDENTIAL & PROPRIETARY INFORMATION**

Premarket Notification - Benfotiamine/Alpha-Lipoic Acid Combination 225 mg (75 mg Benfotiamine & 150 mg Alpha-Lipoic Acid) & Benfotiamine/Alpha-Lipoic Acid Combination 450 mg (150 mg Benfotiamine & 300 mg Alpha-Lipoic Acid)

Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-800)  
Center for Food Safety and Applied Nutrition  
Food and Drug Administration  
5100 Paint Branch Parkway  
College Park, MD 20740-3835

2006-890

Dear Sir or Madam:

Notice is hereby given pursuant to the requirements of 21 CFR 190.6 of the Food & Drug Administration, Department Of Health & Human Services (Part 190--Dietary Supplements) of the intent of The Pryde Company to introduce and be the distributor of a new dietary ingredient, Benfotiamine/Alpha-Lipoic Acid Combination ("the ingredient"), into interstate commerce. The ordinary conditions of use are: one 225 mg pill consisting of 75 mg of Benfotiamine and 150 mg of Alpha-Lipoic Acid four times a day by mouth or one 450 mg pill consisting of 150 mg of Benfotiamine and 300 mg of Alpha-Lipoic Acid two times a day by mouth for a total of 300 mg of Benfotiamine and 600 mg of Alpha-Lipoic Acid per day by mouth.

The following journal articles representing a history of use or other evidence establishing the safety of Benfotiamine and Alpha-Lipoic Acid are enclosed with this 75 day Premarket Notification:

1. Benfotiamine in treatment of alcoholic polyneuropathy: an 8-week randomized controlled study (BAP I Study) - Woelke H, Lehl S, Bitsch R, Kopcke W. - Alcohol & Alcoholism (Oxford, Oxfordshire)-1998 Nov-Dec;33(6):631-8
2. Benfotiamine in the treatment of diabetic polyneuropathy--a three-week randomized, controlled pilot study (BEDIP study) - Haupt E, Ledermann H, Kopcke W. - International Journal of Clinical Pharmacology & Therapeutics-2005 Feb;43(2):71-7
3. A Benfotiamine-vitamin B combination in treatment of diabetic polyneuropathy- Stracke H, Lindemann A, Federlin K. - Experimental & Clinical Endocrinology & Diabetes: Official Journal, German Society Of Endocrinology [And] German Diabetes Association-1996;104(4):311-6
4. Effectiveness of different Benfotiamine dosage regimens in the treatment of painful diabetic neuropathy - Winkler G, Pal B, Nagybeganyi E, Ory I, Porochnaeve M, Kempler P. - Arzneimittel-Forschung-1999 Mar;49(3):220-4
5. Therapeutic efficacy of "Milgamma" in patients with painful diabetic neuropathy - Simeonov S, Pavlova M, Mitkov M, Mincheva L, Troev D. - Folia Medica (Plovdiv)-1997;39(4):5-10
6. The sensory symptoms of diabetic polyneuropathy are improved with Alpha-Lipoic Acid: the SYDNEY trial. - Ametov AS, Barinov A, Dyck PJ, Hermann R, Kozlova N, Litchy WJ, Low PA, Nehrlich D, Novosadova M, O'Brien PC, Reljanovic M, Samigullin R, Schuette K, Stokov I, Tritschler HJ, Wessel K, Yakhno N, Ziegler D; SYDNEY Trial Study Group - Diabetes Care-2003 Mar;26(7):2227

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7. Effects of treatment with the antioxidant alpha-lipoic acid on cardiac autonomic neuropathy in NIDDM patients. A 4-month randomized controlled multicenter trial (DEKAN Study). *Deutsche Kardiale Autonome Neuropathie* - Ziegler D, Schatz H, Conrad F, Gries FA, Ulrich H, Reichel G. - *Diabetes Care*-1997 Dec;20(12):1918-20
8. Alpha-lipoic acid in the treatment of diabetic polyneuropathy in Germany: current evidence from clinical trials - Ziegler D, Reljanovic M, Mehnert H, Gries FA-*Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association*-1999;107(7):421-30
9. Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a meta-analysis - Ziegler D, Nowak H, Kempler P, Vargha P, Low PA-*Diabetic Medicine: a journal of the British Diabetic Association*-2004 Feb;21(2):114-21
10. Treatment for diabetic mononeuropathy with alpha-lipoic acid - Tankova T, Cherninkova S, Koev D - *International Journal of Clinical Practice*-2005 Jun;59(6):645-50
11. Thioctic acid for patients with symptomatic diabetic polyneuropathy: a critical review - Ziegler D - *Treatments in Endocrinology*-2004;3(3):173-89

It should be noted that in reference #1, Benfotiamine in treatment of alcoholic polyneuropathy: an 8-week randomized controlled study (BAP I Study), on page 636 in the paragraph labeled "Compliance and side effects", the authors state:  
"No adverse events related to treatment occurred."

It should be noted that in reference #2, Benfotiamine in the treatment of diabetic polyneuropathy - a three-week randomized, controlled pilot study (BEDIP study), on page 71 in the paragraph labeled "Abstract", the authors state:  
"No side effects attributable to Benfotiamine were observed."

It should be noted that in reference #3, A Benfotiamine-vitamin B combination in treatment of diabetic polyneuropathy, on page 311 in the paragraph labeled "Summary", the authors state:  
"Therapy-specific adverse effects were not seen."

It should be noted that in reference #4, Effectiveness of different Benfotiamine dosage regimens in the treatment of painful diabetic neuropathy, on page 223 in the paragraph labeled "3. Results", the authors state:  
"No side-effects were observed, which needed neither cessation of drug therapy, nor diminution of the fixed dosage regimen."

It should be noted that in reference #5, Therapeutic efficacy of "Milgamma" in patients with painful diabetic neuropathy, on page 5 in the paragraph labeled "Summary", the authors state:  
"No adverse reactions were observed following the administration of the medication."

It should be noted that in reference #6, The sensory symptoms of diabetic polyneuropathy are improved with Alpha-Lipoic Acid: the SYDNEY trial, on page 773 in the paragraph labeled "Adverse events", the authors state:  
"No adverse event (AE) was judged to be causally related to the trial medication."

It should be noted that in reference #7, Effects of treatment with the antioxidant alpha-lipoic acid on cardiac autonomic neuropathy in NIDDM patients. A 4-month randomized controlled multicenter trial (DEKAN Study), on page 369 in the paragraph labeled "Results", the authors state:  
"No differences between the groups were noted regarding the rates of adverse events."

It should be noted that in reference #8, Alpha-lipoic acid in the treatment of diabetic polyneuropathy in Germany: current evidence from clinical trials, on page 428 in the paragraph labeled "Conclusions", the authors state:

"Clinical and postmarketing surveillance studies have revealed an excellent safety profile of the drug"

It should be noted that in reference #9, Treatment of symptomatic diabetic polyneuropathy with the antioxidant alpha-lipoic acid: a meta-analysis, on page 119 in the paragraph labeled "Discussion", the authors state:

"Moreover, treatment with a-lipoic acid was associated with rates of adverse events not exceeding those of placebo."

It should be noted that in reference #10, Treatment for diabetic mononeuropathy with alpha-lipoic acid, on page 647 in the paragraph labeled "Results", the authors state:

"The drug was well tolerated; the patients did not report any side effects during the treatment period."

It should be noted that in reference #11, Treatment for diabetic mononeuropathy with alpha-lipoic acid, on page 186 in the paragraph labeled "6. Tolerability of Thioctic Acid in Diabetic Neuropathy", the authors state:

"With respect to the large experience in a high number of patients treated with Thioctic Acid in Germany (far more than 2 million), the incidence of adverse drug reactions reported so far seems to be very low"

Thank you for your time and consideration in this matter.

Sincerely,



Eric J. Scopp  
V.P. of Operations  
escopp@prydepharm.com

# THE PRYDE COMPANY

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Corp: 258 S.E. 6th Ave. Ste.12, Delray Beach, FL 33483  
Sales: 21 N. Brown Ave. Orlando, FL 32801  
407.897.0950 • Toll Free: 866.PRYDE10 • Fax: 407.228.4936

January 16, 2006

**CERTIFIED MAIL - RETURN RECEIPT REQUESTED  
TRADE SECRET - CONFIDENTIAL & PROPRIETARY INFORMATION**

Premarket Notification - Benfotiamine 75 mg & Benfotiamine 150 mg

Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-800)  
Center for Food Safety and Applied Nutrition  
Food and Drug Administration  
5100 Paint Branch Parkway  
College Park, MD 20740-3835

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Notice is hereby given pursuant to the requirements of 21 CFR 190.6 of the Food & Drug Administration, Department Of Health & Human Services (Part 190--Dietary Supplements) of the intent of The Pryde Company to introduce and be the distributor of a new dietary ingredient, Benfotiamine ("the ingredient"), into interstate commerce. The ordinary conditions of use are: one 75 mg pill of Benfotiamine four times a day by mouth or one 150 mg pill of Benfotiamine two times a day by mouth per day for a total of 300 mg of Benfotiamine per day.

The following journal articles representing a history of use or other evidence establishing the safety of Benfotiamine are enclosed with this 75 day Premarket Notification:

1. Benfotiamine in treatment of alcoholic polyneuropathy: an 8-week randomized controlled study (BAP I Study) - Woelk H, Lehl S, Bitsch R, Kopcke W. - *Alcohol & Alcoholism (Oxford, Oxfordshire)*-1998 Nov-Dec;33(6):631-8
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Eric J. Scopp  
V.P. of Operations  
escopp@prydepharm.com