

Memorandum

0037 6 FEB -2 P2:25

Date: JAN 6 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

Firm: Louis Montgomery Enterprises

Date Received by FDA: October 11, 2005

90-Day Date: January 9, 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

RPT309



DEC 23 2005

Mr. Louis Montgomery
Louis Montgomery Enterprises
6542 Hypoluxo Road, Suite 114
Lake Worth, Florida 33467

Dear Mr. Montgomery:

This is to inform you that the notification, dated October 7, 2005, 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 October 11, 2005. Your notification concerned the substance that you identified as "Benfotiamine" which you intend to market as a new dietary ingredient.

According to your notification, "Benfotiamine" will be marketed in a tablet containing 150 mg of this new dietary ingredient. The conditions of use that will be suggested or recommended on the label include "users supplement their diets with 1-4 capsules per day (150-600) of Benfotiamine" or as recommended by their health care professionals...."

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.

It is not readily apparent whether "Benfotiamine" that 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" is a "dietary ingredient" within the meaning of 21 U.S.C. 321(ff)(1).

FDA was unable to determine the composition of your "Benfotiamine". Your notification includes a copy of a US Patent assigned to Ito et al., Sankyo Kabushiki Kaisha, Tokyo, Japan, which describes three (3) chemical syntheses for a group of S-benzoylthiamine-0-monophosphate compounds that include sodium and calcium salts. Since the patent covers compounds from a group that includes several chemical syntheses and the resulting sodium and calcium salts, the composition of the material that is to be manufactured is not clear. In addition, the relationship between the material that is to be manufactured and the materials marketed in other countries is not clear.

Your notification will be kept confidential for 90 days after the filing date of October 11, 2005. 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,



for

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

11/2005
O.B./FOA

Pre-Market Notification Submission
for
S-BENZOYLTHIAMINE O-MONOPHOSPHATE
(BENFOTIAMINE)

Number 3 of 3

October 7, 2005

CAIMS
2005-6756

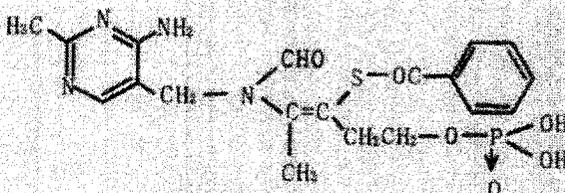
Submitted by: Louis Montgomery Enterprises

October 7, 2005

Food and Drug Administration
Division of Standards and Labeling Regulations
Office of Nutritional Products, Labeling, and Dietary Supplements
(HFS-820) Center for Food Safety and Applied Nutrition
5100 Paint Branch Parkway
College Park, MD, 20740-3835

1. Name/address of the distributor of the New Dietary Ingredient:
 - 1.1. Louis Montgomery Enterprises, 6542 Hypoluxo Road, Suite 114, Lake Worth, FL 33467.
2. The name of the subject New Dietary Ingredient:
 - 2.1. S-benzoylthiamine-O-monophosphate, common name **benfotiamine**, chemical formula, molecular formula and structure depicted below:

White crystals or crystalline powder.
FORMULA: C₁₉H₂₃N₄O₆PS MOLECULAR FORMULA: 466.45



MELTING POINT: about 200°C (with decomposition)

3. At or shortly after the termination of the 75-day pre-market notification period, if you concur with my conclusion that benfotiamine may reasonably be expected to be safe, I intend to:
 - 3.1. Manufacture and distribute benfotiamine **capsules** produced in an FDA-certified facility under GMP conditions. These capsules, intended for oral use, will contain **150mg. of benfotiamine** and no other active ingredients.
 - 3.2. The label will recommend users supplement their diets with 1-4 capsules per day (150mg. – 600mg.) of benfotiamine, or as recommended by their health care professionals, to effectively and safely increase durable levels of active thiamine in their tissues and viscera.

4. History of use or other evidence that benfotiamine, when used as recommended or suggested on the label, will reasonably be expected to be safe:

4.1. On November 13, 1962 the United States Patent Office issued US Patent Number 3,064,000 (See Tab 1) for S-BENZOYLTHIAMINE O-MONOPHOSPHATE AND A PROCESS FOR PREPARING THE SAME. To quote from two locations in the patent:

4.1.1. "S-benzoylthiamine O-monophosphate of this invention has lower toxicity than thiamine hydrochloride as shown in Table III." (See page 2, column 3 of the patent, just above Table III.)

4.1.2. "S-benzoylthiamine O-monophosphate of this invention is prominent in that it may be readily converted to active form of thiamine in the body and it may be readily utilized in the body as the thiamine source. Moreover, this thiamine derivative may be readily absorbed in the body maintaining thiamine levels of viscera high for a long period of time." (See page 2, column 3 of the patent, just below Table III.)

4.2. Based on laboratory mouse LD50 tests, benfotiamine has a more favorable toxicological profile than many of the other B-complex vitamins by a wide margin, including especially the more common vitamin B-1 precursor/provitamin: thiamine hydrochloride. (See the table below and the toxicology sheets at Tab 2)

Compound	Vitamin	LD50 Results (Oral, Lab Mice)
S-benzoylthiamine O-monophosphate (benfotiamine)	B-1	15,000 mg/kg
Thiamine hydrochloride	B-1	8,224 mg/kg
Niacin	B-3	3,720 mg/kg
Adenine	B-4	783 mg/kg
Calcium Pantothenate	B-5	10,000 mg/kg
Pyridoxine Hydrochloride	B-6	5,500 mg/kg
Folic Acid	B-11 (Folate)	10,000 mg/kg
Cyanocobalamine	B-12	5,000 mg/kg

(Riboflavin (B-2) was not included in the table because all available data for riboflavin was based on lab rats vs. mice (10,000 mg/kg))

- 4.3. According to the scientific paper *Pharmacokinetics of Thiamine Derivatives Especially of Benfotiamine*, authored by Dr. D. Loew of Wuppertal, Germany, and published in the International Journal of Clinical Pharmacology and Therapeutics, Vol. 34, No. 2 – 1996 (pgs. 47-50) (**See Tab 3**):
- 4.3.1. "Due to their greater bioavailability and better tissue passage **lipid-soluble thiamine analogues like benfotiamine are preferable to water-soluble thiamine derivatives...**" (pg. 49, column 2)
- 4.3.2. "Due to its excellent pharmacokinetic profile and to its **excellent tolerability** benfotiamine should be preferred..." (pg. 49, last para.)
- 4.4. For me the most convincing history of use data I found regarding benfotiamine (**See Tab 4**) was obtained from the Bundesinstitut für Arzneimittel und Medizinprodukte (The German Federal Institute for Drugs and Medical Devices) from whom I learned:
- 4.4.1. Benfotiamine has been available at pharmacies in Germany without prescription since 1978.
- 4.4.2. Typical daily oral dosages of benfotiamine range from 50mg. to an authorized maximum of 900mg.
- 4.4.3. Based only on prescription data for one benfotiamine preparation sold in Germany (Milgamma Mono), there were 2.4 million defined daily dosages prescribed during the calendar year 2002. (One may infer that the actual annual number of defined daily dosages of benfotiamine consumed is much higher than 2.4 million, as it is widely available without a prescription from pharmacies throughout Germany.)
- 4.4.4. Within their database, **in the 27 years since 1978**, there have been only **18 adverse reactions reported** involving benfotiamine single component preparations, and in **only 10** of those reports was **benfotiamine suspected** as the possible cause. In the other 8 reports, benfotiamine was reported as a concomitant compound in the list of other compounds involved. Of the 10 reports where benfotiamine was suspected as the causal agent, 7 reports indicated transient headache as the adverse reaction. (**Please see Tab 4 for my inquiry to BfArM and their complete response.**)
- 4.4.5. To quote from their response: "With regard to benfotiamine, routine pharmacovigilance has been performed using data from different sources (spontaneous ADR reports, periodic safety update reports, scientific literature). In doing so, **no safety signals pertaining to benfotiamine ...have been identified.**"

4.4.6. As needed, further elaboration on this data may be obtained from Dr. Joerg Seebeck, MD, Dept. of Pharmacovigilance/BfArM, Tel. 011 49 228 207 3796, Fax 011 49 228 207 3515.

4.5. I offer the reference at **Tab 5** as further evidence that daily dosages of benfotiamine in the 600mg. are well-tolerated without reports of adverse reactions.

4.6.

4.7.

4.8. I have learned that benfotiamine is marketed by a number of firms worldwide in markets from Japan and throughout Asia as well as most of Western and especially Eastern Europe and Russia. Though it would be impractical to cite and provide photocopies of all the literature I have reviewed to prepare this submission, I will certify that I have not uncovered any reports in any of the literature pertaining to benfotiamine that would lead one to assume that benfotiamine cannot reasonably be expected to be safe. To the contrary, benfotiamine is consistently cited in the literature as being highly tolerable and very non-toxic.

5. Based on the evidence provided/cited herein, I hope you will agree with my conclusion that benfotiamine can reasonably be expected to be safe. It is my intention to make this preferred thiamine precursor/provitamin available to Americans as conveniently and inexpensively as possible.



Louis A. Montgomery

Table of Contents

1

US Patent Number 3,064,000
S-BENZOYLTHIAMINE O-
MONOPHOSPHATE AND A
PROCESS FOR PREPARING
THE SAME

2

Toxicology Data, various B-
complex vitamins

3

*Pharmacokinetics of Thiamine
Derivatives Especially of
Benfotiamine, Dr. D. Loew*

4

Correspondence to/from the
German Institute for Drugs and
Medical Devices

5

Clinical Trial results
administering 600mg. per day
of benfotiamine