DEPARTMENT OF HEALTH & HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Public Health Service

Memorandum

Date APR - 4 2000

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From Chief, Dietary Supplements Branch, Division of Compliance & Enforcement, Office of Nutritional Products, Labeling, and Dietary Supplements, HFS-811

Subject 75-day Premarket Notification for New Dietary Ingredient

To Dockets Management Branch, HFA-305

New Dietary Ingredient:	Vincamine
Firm:	General Nutrition Corporation
Date Received by FDA:	January 20, 2000
90-day Date:	April 18, 2000

In accordance with the requirements of section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification for the aforementioned new dietary ingredient should be placed on public display in docket number 95S-0316 after April 18, 2000.

Robert J. Moore, Ph.D.

95S-0316

RPT62

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC 20204

APR - 3 2000

Susan Trimbo, Ph.D.
Vice President, Scientific Affairs
General Nutrition Corporation
300 Sixth Avenue
Pittsburgh, Pennsylvania 15222

Dear Dr. Trimbo:

This letter is in response to your letter to the Food and Drug Administration (FDA) dated January 12, 2000, making a submission for a new dietary ingredient pursuant to 21 U.S.C. 350b(a)(2) (section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act). Your letter notified FDA of your intent to market a product containing a new dietary ingredient named vincamine. Your submission was received by FDA on January 20, 2000. Your submission will be kept confidential for 90 days from the date of receipt, and after April 18, 2000, your submission will be placed on public display at Dockets Management Branch (Docket No. 95S-0316). Commercial and confidential information in the notification will not be made available to the public.

21 U.S.C. 350b(a)(2) requires that a manufacturer or distributor of a dietary supplement that contains a new dietary ingredient 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 section 350b(a)(2), there must be a history of use or other evidence of safety establishing that the 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 deemed 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.

The submission contained five papers that reported the results of studies conducted in human patients with cerebrovascular insufficiency to test the therapeutic effects of vincamine. The studies in this submission, when considered along with the information in your previous submission, appear to provide an adequate basis that a dietary supplement containing vincamine will reasonably be expected to be safe in healthy adults who would consume dietary supplements that provide up to 20 milligrams of vincamine per day for up to 6 months. However, the studies do not appear to be sufficient to establish that a dietary supplement containing vincamine, when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe for children.

Moreover, the information you submitted does not address the safety of chronic, long-term use (that is, use in excess of 6 months, the longest study duration reported in the information you provided). Therefore, a dietary supplement containing vincamine that is labeled for use by children or for periods in excess of 6 months may be 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).

Please contact us if you have questions concerning this matter.

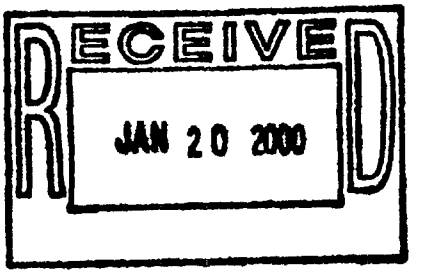
Sincerely,

John B. Foret

John B. Foret
Director
Division of Compliance and Enforcement
Office of Nutritional Products, Labeling,
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

GNC LiveWell.

Susan Trimbo, Ph.D.
Vice President
Scientific Affairs



January 12, 2000

Lynn A. Larsen Ph.D.
Director
Division of Programs and Enforcement Policy
Office of Special Nutritionals
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C. Street (HFS-450)
Washington, D.C. 20204

Re: Vincamine

Dear Dr. Larsen;

This letter is in response to your September 13 letter to GNC, which expresses concerns about the safety of vincamine. We have carefully reviewed your correspondence and wish to provide a response to your comments and submit additional information for your consideration.

Vincamine has been used extensively in an oral dosage form since 1969. A number of scientific publications, including clinical trials of varying design, appear in the literature dating back to the mid 1970s. We submit three published clinical trials which monitored both the clinical tolerance of vincamine (or time-released version) as well as serum chemistry values as part of the overall safety evaluation. These studies are summarized in the attached table and full copies (plus translations) are provided for your review. The findings are representative of those reported in other publications. All of the studies provided evaluated vincamine given orally at a dose of 60 mg per day. (GNC has an interest in marketing a 30-mg tablet which would be taken once per day.) Collectively, these studies establish that the side effects of oral vincamine use (when taken for up to 12 weeks) are generally not classified as serious and primarily affect the gastrointestinal tract.

In addition to the trials cited above, we have included two open trials involving large numbers of subjects treated for up to 6 months. These trials report tolerance data that are consistent with those reported in the double-blind, placebo-controlled trials summarized in the attached table. Overall the percentage of individuals reporting side-effects is within the range reported in controlled trials for other dietary supplements such as ginkgo biloba extract.

General Nutrition Corporation, 300 Sixth Avenue, Pittsburgh, PA 15222
Tel: (412) 338-8844 Fax: (412) 338-8954

With regard to the toxicological data provided in our June 28, 1999 submission, additional explanation of the findings is necessary. A number of the publications examined the effects of intravenous administration of vincamine. It should be noted that the side-effects (type, severity and incidence) associated with vincamine use in these studies is linked to the route of infusion, infusion rate and dose. The enclosed study by Pirani et al (1978) provides data in support of this point. Furthermore, a number of the intravenous studies examined the effects of dosages up to 60mg . One would expect effects of the compound to be more pronounced compared to orally administered vincamine at the same dose due to the higher bio availability of an intravenously administered compounds. Together these findings, along with the other safety data submitted, establish that this dietary ingredient, when used under the conditions suggested in the labeling of the dietary supplement is reasonably expected to be safe.

We respectfully request that you reconsider the safety information provided herein. General Nutrition Corporation remains interested in marketing Vincamine as a dietary supplement as provided for under Section 8 of the Dietary Supplement Health and Education Act of 1994. An original and two copies of this correspondence and supporting documentation are provided.

Sincerely yours,

Susan Trimbo, Ph.D.
Vice President, Scientific Affairs

ST/tf
Enclosures
Cc: Ron Thompson

Vincamine Studies

Double-Blind, Placebo-Controlled

Author	Study Design/ Population	Dose of Administration Form of Administation Route of Adminsitration	Treatment Duration	Safety/Tolerance Findings
Mikus				
Arzneimittelforschung 1978 28(11): 2165-2168	• Double-blind, placebo-controlled. • 26 subjects (16 men: 10 women) cerebrovascular insufficiency. • Age range 46-76 years	• 60mg/day • vincamine cromesilate • oral	4 weeks	• No change in body weight, blood pressure, EKG, liver or renal function. • Low rate of side-effects. • No change in most lab values: Reduction in serum cholesterol (within normal range) • 2 reports of fatigue, 1 report of itching, 1 report of dry mouth.
Schenker				
Praxis 1979 68: 1005-1011	• Double blind-placebo-controlled • 50 patients cerebrovascular insufficiency. • Age range 55-89 years	• 60mg/day • vincamine (time release) • oral	4 weeks	• mild, transitory gastrointestinal complaints in 4 subjects.
Fischoff et al				
Neuropsychobiology 1996 34; 29-35	• Multicenter, double blind, placebo controlled • 152 patients cerebrovascular insufficiency (71 patients completed each treatment.) • Age range 50-85 years	• 60mg/day • vincamine(time realease) • oral	12 weeks	• no effect on blood pressure or lab values • triglycerides declined more in vincamine group • 19 patients reported AEs (12 vincamine treated)- diarrhea, insomnia, vertigo, hypotension, nervousness, vomiting, and nausea.
Open Studies				
Peritti et al				
ClinTer 1981 97(2) 137-145	• Multicenter, open 1854 outpatients with cerebrovascular insufficiency completed protocol (791 Men, 1063 woman) • Age range 51-96 years	• 60 mg/day vincamine • vincamine HCI • oral	6 months	• 27 subjects out of 2440 discontinued due to side effects (gastrointestinal) • Mild transient side-effects in 135 of 1854 patients • Excellent tolerance
Alescio e tal				
Minerva Med 1978 69(31):2095-2113	• Multicenter, open-label • 828 patients (399 men; 429 woman) cerebrovascular insufficiency • Age range 45-87 years	• 60mg/day • vincamine • oral	Up to 60 days	• good tolerance • 5 discontinued treatment due to GI complaints or allergic skin reactions. • No significant effect on blood chemistry. • Normalizationof blood pressure. • EKG abnormal in 1 subject