DEPARTMENT OF HEALTH & HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Public Health Service

Memorandum

Date APR 19 1999

From Senior Regulatory Scientist, Regulatory Branch, Division of Programs & Enforcement Policy (DPEP), Office of Special Nutritionals, HFS-456

Subject 75-day Premarket Notification for New Dietary Ingredient

To Dockets Management Branch, HFA-305

New Dietary Ingredient:	vinpocetine
Firm:	General Nutrition Corporation
Date Received by FDA:	April 16, 1999
90-day Date:	July 13, 1999

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 July 13, 1999.

Robert J. Moore

Robert J. Moore, Ph.D.

95S-0316

RPT 47

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC 20204

8961 '99 APR 20 P2:10

APR 19 1999

Ronald Thompson, Ph.D.
Vice President, Product Development
General Nutrition Corporation
300 Sixth Avenue
Pittsburgh, Pennsylvania 15222

Dear Dr. Thompson:

This is to notify you that your submission pursuant to section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act) dated April 12, 1999, concerning the marketing of a substance that you assert is a new dietary ingredient (i.e., vinpocetine) was received by the Food and Drug Administration (FDA) on April 16, 1999. Your submission will be kept confidential for 90 days from the date of receipt, and after July 13, 1999, 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.

Please contact us if you have questions concerning this matter.

Sincerely,

Robert J. Moore, Ph.D.
Senior Regulatory Scientist
Division of Programs and Enforcement Policy
Office of Special Nutritionals

GNC LiveWell.

RECEIVED 4/16/99

1962 '99 APR 20 P2:10

April 12, 1999

Office of Special Nutritionals
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street (HFS-450)
Washington, DC 20204

Dear Ma'am or Sir:

Pursuant to Section 8 of the Dietary Supplement Health and Education Act of 1994, General Nutrition Corporation ("GNC") located at 300 Sixth Avenue, Pittsburgh, PA 15222 wishes to notify the Food and Drug Administration that GNC will market a new dietary ingredient, Vinpocetine, a derivative of vincamine, which is an extract of vinca minor (periwinkle). Accordingly, enclosed please find an original and two (2) copies of this notification.

The dietary supplement which contains Vinpocetine, will consist of 5mg of Vinpocetine in a tablet or capsule which will be suggested to be taken one (1) time per day.

Attached please find the scientific studies and other information which establish that this dietary ingredient, when used under the conditions suggested in the labeling of the dietary supplement, is reasonably expected to be safe. This information includes:

(1) Product Specification & Process Manufacturing

(2) Toxicity Studies

(3) Clinical Research Study

Very truly yours,

Ronald Thompson, Ph.D.
Vice President, Product Development

Enclosures

General Nutrition Corporation, 300 Sixth Avenue, Pittsburgh, PA 15222
Tel: (412) 288-4600

Product Specification & Process Manufacturing

VINPOCETINE

NOMENCLATURE

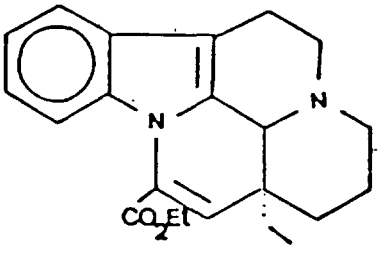
International Nomenclature (INN): Vinpocetine, Vinpocetinum
Chemical Name: (3α, 16α) eburnamenine -14-carboxylic acid ethyl ester

Other Names: Ethyl apovincaminate, Cavinton™, Ceractin™ (ref.: Merck Index, XII, Nº 10128).

DESCRIPTION

Vinpocetine is a white or slightly yellow crystaline powder, odourless, soluble in chloroform and in methylene chloride, slightly soluble in alcohol and methanol, insoluble in water.

Structural Formula:

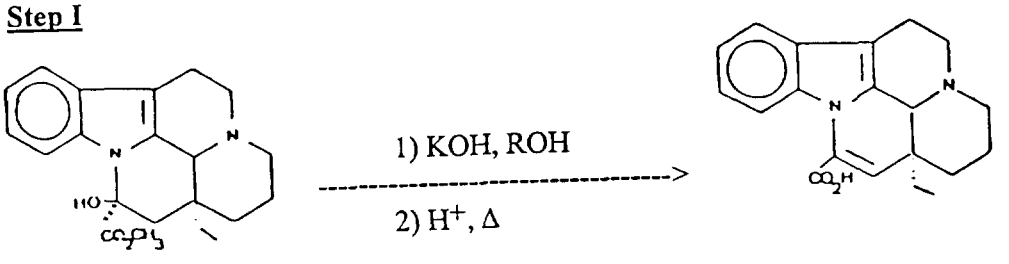


Molecular Formula: $C_{22}H_{26}N_2O_2$
Molecular Weight: 350.46
Chirality: (+)Vinpocetine

MANUFACTURE. SYNTHESIS METHOD

The steps are as follows:

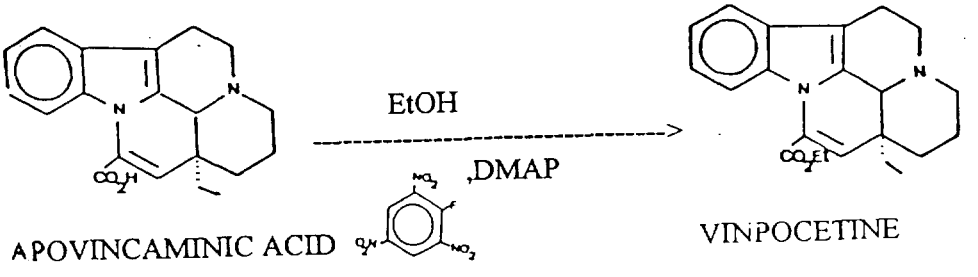
Step I



VINCAMINE

APOVINCAMINIC ACID

Step II



APOVINCAMINIC ACID

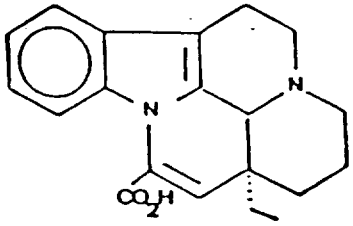
VINPOCETINE

See Pat. ES 549.105, by reaction between apovincaminic acid and ethyl alcohol catalized by 4-dimethylamine pyridine and 2,4,6-trinitro-fluorobenzene. Apovincaminic acid was obtained by vincamine with potassium hydroxide in methyl alcohol.

Purification steps: Vinpocetine is purified by silica gel chromatography, using methylene chloride. The solvent is then eliminated and the product is crystallised in ethanol (99.6%).

QUALITY CONTROL DURING MANUFACTURE

Starting material: Apovincaminic acid



Apovincaminic acid

$C_{20}H_{22}N_2O_2$: 322.43

DESCRIPTION

Apovincaminic acid is a white or slightly yellow powder, odourless.

IDENTIFICATION

Mass spectrum, m/e: 322 (M^+), 293, 252, etc.
Dragendorff test: complies.
Melting point: 248-250°C (dc).
Specific rotation: +85° (0.1%, 1N NaOH).

PURITY TEST

High Performance Liquid Chromatography (HPLC): Weigh 0.1g of apovincaminic acid (test solution) and dilute in 20 ml of 1N NaOH and 80 ml of acetonitrile (HPLC) to make 100 ml. Weigh 0.01g of apovincaminic acid (standard solution), dilute in 20 ml of 1N NaOH and 80 ml of acetonitrile (HPLC) to make 100 ml.

Inject 50 µl of the prepared solutions (test and standard solutions), in the chromatographic conditions required. Retention time: 1.7 min ± 10%. Retention time of apovincaminic acid test must be the same as that of the standard reference.

Chromatographic conditions:
Detector: UV spectrophotometer (wavelength: 280 nm).
Column: Spherisorb C18 ODS2 5µm (25x0.46 cm).
Mobile Phase: Ammonium acetate buffer/acetonitrile (3:7). Ammonium acetate buffer: 0.2M in water (HPLC grade).
Flow: Adjust the flow so that the apovincaminic acid peak appears aprox. at 2 minutes.

LOSS ON DRYING

Not more than 0.5% (on dry).

ACIDIMETRIC ASSAY IN NON AQUEOUS SOLVENTS

Weigh accurately about 0.3 g (W g) of apovincaminic acid, previously dried. Dissolve in 30 ml of a mixture of acetic anhydride and glacial acetic acid (1:1), add 0.2 ml of crystal violet solution and tritrate with 0.1N perchloric acid (a ml). In the same manner make a measurement of the blank (b ml), and make any necessary corrections.

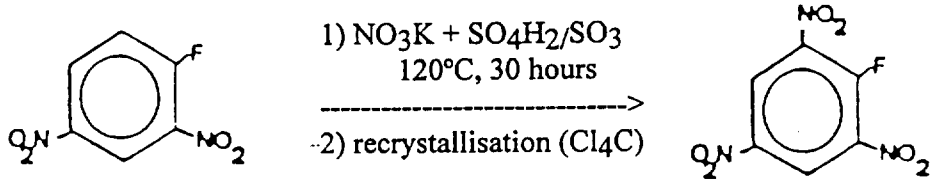
$$\% \text{ of apovincaminic acid: } \frac{(a-b) \times f \times 3{,}2243}{W \times 100}$$

f: Perchloric acid factor 0.1N.

Analysis: Not more than 101.5% and not less than 98.5% (on dry).

REGENTS AND SOLVENTS

-Ethyl alcohol: Merck quality, absolute for synthesis (Art. 818761).
-DMAP (4-dimethyl amino pyridine): Fluka quality (Art. 39405).
-FTNB (1-fluor-2,4,6-trinitrobenzene): Quality: M.P.: 122-123°C; centesimal composition, calculated: C,31.19; h, 0.86; N, 18.19. Measured: C, 30.97; h, 0.96; N, 18.40. Synthesised in the laboratory as follows:



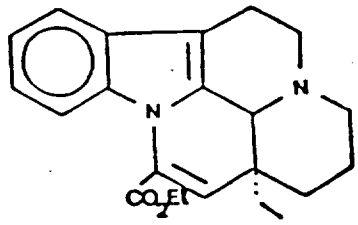
A B

-1-fluor-2,4,6-trinitrobenzene (A): Fluka quality (Art. 42080).
-NO_3K (Potassium nitrate): Merck quality, very pure (Art. 5061).
-SO_4H_2 (sulphuric acid): Merck fuming quality of 30% SO_3 (Art. 721).

-Methylene chloride: Merck quality for synthesis, stabilised with 0.2% of ethyl alcohol (Art. 82271).

CHEMICAL DEVELOPMENT OF THE PRODUCT (vinpocetine)

Evidence on the structure of vinpocetine
Characteristics of vinpocetine std



$C_{22}H_{26}N_2O_2$: 350.46

Vinpocetine assay: Not less than 98.5% and not more than 101.5% (on dry).

DESCRIPTION

Vinpocetine is a white or slightly yellow crystalline powder, odourless. Soluble in chloroform and in methylene chloride, slightly soluble in alcohol and methanol, insoluble in water.

IDENTIFICATION

Draggendorf Test: Dissolve 0.05 g of vinpocetine in 5 ml of 0.1N hydrochloric acid TS. Add 2 or 3 drops of Draggendorf TS. An orange precipitate should appear.
Draggendorf TS: Dissolve 0.85 g of bismuth subnitrate in 10 ml of acetic acid and add 40 ml of water (solution A). Dissolve 8 g of potassium iodide in 20 ml of water (solution B). Immediately before use mix equal volumes of solutions A, B and glacial acetic acid. Store solutions A and B in light-protected recipients, in the refrigerator.

UV Spectrum: In methanol (1-10000) It has maxima at 228-230 nm, 273-275 nm and, 313-320 nm.

IR Spectrum (Nujol): 3060, 1630, 1605, 1480, 750, etc. cm^{-1}.

1H-NMR Spectrum (CDCl3), δ: 1.00 (t 3H, 21-$\underline{CH_3}$), 1.35 (t 3H, 24-$\underline{CH_3}$), 4.48 (q 2H, 23-$\underline{CH_2}$), 6.10 (s 1H, $\underline{H}_{15}$), 7.3-7.5 (m 4H, H_9, H_{10}, H_{11}, H_{12}), etc. ppm.

13C-NMR Spectrum (CDCl3), δ: 162.85; 133.62; 130.52; 128.65; 128.00; 127.34; 121.27; 119.72; 117.72; 112.12; 108.15; 61.17; 55.21; 50.98; 44.42; 37.14; 28.25; 26.79; 19.89; 15.86; 13.76; 8.30 ppm.

PURITY TESTS

Colour and appearance of the solution: Dissolve 1g of vinpocetine in 100 ml of chloroform p.a. The colour of the test solution must not be more intense than the colour of the reference solution P9 of the European Pharmacopoeia. Vol. I, V.6.2.

Sulphuric Ashes: According to the European Pharmacopoeia, Vol. I, V. 3.2.14.

Heavy Metals: According to the European Pharmacopoeia, Vol. I, V.3.2.8. The content of metal impurities is determined by reaction with the sulphur ion under the specified conditions. It is quantified by comparison to a std lead solution. Specification: not more than 10 ppm.

High Performance Liquid Chromatography (HPLC): Weigh 0.1g of vinpocetine and dilute in HPLC acetonitrile, to 100 ml (test solution). Separately, weight 0.01g of vinpocetine standard and dilute in HPLC acetonitrile, to 100 ml (standard solution).

Inject separately 50 µl of the solutions prepared before (test and standard solutions), in the chromatographic conditions required.

Chromatographic conditions:
Detector: UV spectrophotometer (wavelength: 280 nm)
Column: Spherisorb C18 ODS2 5µm (25x0.46 cm).
Mobile Phase: Ammonium acetate tampon/acetonitrile (3:7). Ammonium acetate tampon: solution 0.2M in water (HPLC grade)
Flow: Adjust the flow so that the vinpocetine peak appears at aprox. 13 minutes.

Individual related substances: apovincaminic acid: not more than 0.1%; apovincamine: not more than 0.1%; ethyl vincaminate: not more than 0.2%; ethyl apovincinate: not more than 0.1%. Other related substances: each one not more than 0.1%. TOTAL RELATED SUBSTANCES: NOT MORE THAN 0.5%.

Residual solvents: ethyl alcohol: not more than 200 ppm, methylene chloride: not more than 100 ppm.

LOSS ON DRYING

Not more than 0.5% (1g at 100°C, 4h and 700 Torr).

ACIDIMETRIC ASSAY IN NON AQUEOUS SOLVENTS

Weight accurately about 0.3 g (W g) of vinpocetine, previously dried. Dissolve in 30 ml of a mixture of acetic anhydride and glacial acetic acid (1:1), add 0.2 ml of crystal violet solution and tritrate with 0.1N perchloric acid (a ml). In the same manner make a measurement of the blank (b ml), and make any necessary corrections.

$$\% \text{ of vinpocetine: } \frac{(a-b) \times f \times 3{,}5046}{W \times 100}$$

f: Perchloric acid factor 0.1N.

Analysis: Not more than 101.5% and not less than 98.5% (on dry).

CHIRALITY

$[\alpha]_D^{20}$: +142° to +147° (c=1%, in chloroform); +127° to +130° (c=1%, in N,N-dimethylformamide).

IMPURITIES

The known potential impurities of vinpocetine are:

APOVINCAMINIC ACID
ETHYL VINCAMINATE
APOVINCAMINE
ETHYL APOVINCINATE

STABILITY

Manufacturing Batch: CV/890101
Manufacturing Date: January, 1989
Amount of production: 250 Kg

Conditions: 25°C ± 2 and humidity: 60% ± 5

TIME (*) (months)	1	3	6	12	24	36
COLOUR	<P_9	<P_9	<P_9	<P_9	<P_9	<P_9
$[\alpha]_D^{20}$	+145°	+145°	+145°	+145°	+145°	+145°
LOSS ON DRYING	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
PURITY (Titration)	99.5%	99.5%	99.5%	99.5%	99.5%	99.4%
Rel. S. (HPLC)	complies	complies	complies	complies	complies	complies

Manufacturing Batch: CV/890301
Manufacturing Date: March, 1989
Amount of production: 500 kG

Conditions: 25°C ± 2 and humidity: 60% ± 5

TIME (*) (months)	1	3	6	12	24	36
COLOUR	<P_9	<P_9	<P_9	<P_9	<P_9	<P_9
$[\alpha]_D^{20}$	+145°	+145°	+145°	+145°	+145°	+145°
LOSS ON DRYING	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
PURITY (Titration)	99.7%	99.7%	99.7%	99.7%	99.7%	99.7%
Rel. S. (HPLC)	complies	complies	complies	complies	complies	complies

COVEX
SOCIEDAD ANONIMA

C/. Acero, 25 - Polígono Industrial Sur
Apartado de Correos, n.º 5
28770 Colmenar Viejo - Madrid - ESPAÑ
Tel.: (1) 845 02 00 - Fax: (1) 845 02 08
Tlx.: 47918 COVX E - Cables: COVEX

CERTIFICADO DE ANALISIS
Analysis Certificate

PRODUCTO:
Product **VINPOCETINE BASE**

LOTE N.º:
Batch n.º **CV/960801**

FECHA DE FABRICACION:
Manufacture date **August, 9th 1996**

CANTIDAD:
Quantity **200 KG**

FECHA CADUCIDAD:
Expiry date **August, 2001**

NOMBRE QUIMICO:
Chemical Name

(3α,16α)- eburnamenin-14-carboxylic acid ethyl ester.

DESCRIPCION:
Description

White to slightly yellow crystals or crystalline powder.

SOLUBILIDAD:
Solubility

Soluble in chloroform, insoluble in water.

PUNTO DE FUSION:
Melting Point

ACIDEZ (pH):
Acidity

IDENTIFICACION:
Identification

Complies.

HUMEDAD:
Moisture

0.3% (3h, at 100°C and 600 Torr).

ROTACION EXPECIFICA (α) D :
Specific Rotation

+145° (c: 1%, DMF).

ABSORCION U.V.:
Absortion U.V.

CENIZAS:
Residue on ingnition

0.07% (not more than 0.1%).

SULFATOS:
Sulphates

METALES PESADOS:
Heavy Metals

5 ppm (not more than 10 ppm).

RIQUEZA:
Assay

99.5% (acidimetric assay, on dry).

OTRAS PRUEBAS:
Other Tests

-RELATED SUBSTANCES: Complies.
-IR SPECTRUM: Correspond to vinpocetine std.

OBSERVACIONES: El producto mencionado cumple con
Observations The above product conforms to

DEPARTAMENTO DE CONTROL
Analysis Department