DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

JUN 30 2000

# Memorandum

Date

From Acting Division Director, Division of Standards and Labeling Regulations, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-820

Subject 75-Dau Premarket Notification for New Dietary Ingredients

To Dockets Management Branch, HFA-305

| | |
|---|---|
| New Dietary Ingredient: | *Huperzine A* |
| Firm: | NOW |
| Date Received by FDA | May 23, 2000 |
| 90-Day Date: | August 20, 2000 |

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, The attached 75-day premarket notification for the aftermentioned new dietary ingredient should be placed on public display in docket number

95S-0316 after August 20, 2000

Felicia B. Satchell

Felicia B. Satchell

95S-0316

RPT 75

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Washington, DC 20204

JUN 30 2000

Al Powers
Vice President
NOW Foods
395 S. Glenn Ellyn Road
Bloomingdale, Illinois 60108

Dear Mr. Powers:

This is to notify you that your submission pursuant to section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act dated April 26, 2000, concerning the marketing of a substance that you assert is a new dietary ingredient (i.e., Huperzine A) was received by the Food and Drug Administration on May 23, 2000. Your submission will be kept confidential for 90 days from the date of receipt, and after August 20, 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.

Please contact us if you have any questions concerning this matter.

Sincerely yours,

Felicia B. Satchell

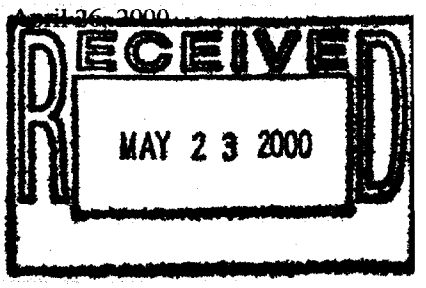
Felicia B. Satchell
(Acting) Division Director
Division of Standards
and Labeling Regulations
Office of Nutritional Products, Labeling
and Dietary Supplements

The Future in Natural Foods

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

70848

April 26, 2000




**RE: Notification of a New Dietary Ingredient**

Dear Sir/Madam,

In compliance with the Dietary Supplement Health and Education Act of 1994, NOW Foods hereby makes its Notification of a New Dietary Ingredient, Huperzine A. Enclosed are two (2) copies of this Notification.

1. Name and Address of the Manufacturer
   **NOW Foods**
   **395 S. Glen Ellyn Rd.**
   **Bloomingdale, IL 60108 USA**

2. Name of the new Dietary Ingredient
   **Huperzine A**

3. Description of the Dietary Supplement containing the new Dietary Ingredient
   **Dietary supplement Brain Elevate contains Huperzine A, an alkaloid compound extracted from the herb *Huperzia serrata* present in a vegetable capsule form.**

   (a) The level of the new dietary ingredient is:
   **25mcg per vegetable capsule**

   (b) The conditions of use suggested on the label are:
   **Suggested use: As a dietary supplement, take 1 Vcap™ 1 to 2 times daily. Do not exceed dosage without the advice of a physician.**

Enclosed please find documentation that establishes this dietary ingredient, Huperzine A, when used under the conditions suggested on the label, will reasonably be expected to be safe. This documentation includes a Certificate of Analysis, toxicity information, review articles and efficacy studies.

An original and two copies of this notice are being filed. Pursuant to 21 CFR 190.6(c), please confirm your receipt of this notice.

Thank you for your time and attention to this matter. If you have any questions or comments, please do not hesitate to contact the undersigned.

Sincerely,
NOW FOODS

Enclosure

Al Powers
Vice President

395 S. GLEN ELLYN ROAD • BLOOMINGDALE, ILLINOIS 60108 • 630/545-9098 • FAX 630/545-0117

# CERTIFICATES OF ANALYSIS

THE FUTURE IN NATURAL FOODS

# Item # 52400

Product Class: 995

## Quality Assurance

**Product Name:** Huperzine A Powder-- 0.1% trituration on $CaCO_3$

**Description:** Huperzine A [(-)-HupA] is a natural compound isolated in an extract of the club moss, *Huperzia serrata*, (also known as *Lycopodium serratum* Thumb) which grows at high elevations and in cold climates. It is a Chinese folk medicine, called *Qian Ceng Ta* and has been used for centuries traditionally to treat fever and inflammation, and recently to improve memory, focus and concentration and helps alleviate memory problems among the elderly. Reports from China, where it is used as a treatment, indicate that Huperzine A is safe and effective. It has other properties such as protecting nerve cells from toxic substances including nerve gas poisons, and from damage produced by strokes and epilepsy. Huperzia extract contains a wide variety of alkaloids, including lycodoline, lycoclavine, and serratinine, as well as the huperzines. Based on the laboratory studies some researchers believe that Huperzine A- a *Lycopodium* alkaloid may be more effective as a treatment of Alzheimer's disease. Scientific research has shown Huperzine A to be potent, selective and reversible inhibitor of AChE (Acetylcholinesterase) – the enzyme that breaks down acetylcholine-a neurotransmitter, with longer duration of action and minimal side effects. In other words Huperzine A has a superior safety and efficacy profile compared to other cholinesterase inhibitors. The chemical name of HupA is: (5R, 9R, 11E)-5-amino-11-ethylidene-5, 6, 9, 10-tetrahydro-7-methyl-5, 9-methanocycloocteno[b]pyridin-2 (1H)-one. Molecular weight is 242.32, ($C_{15}H_{18}N_2O$) (*Merck* Index # 4791). Natural Huperzine A is 3 times more potent than the synthetic forms, which is racemic mixture with 1:1 ratio of (-)-HupA, the natural existing compound, and (+)-HupA (38 fold less potent by itself). Other components like Huperzine B, found in the herb has been suggested to be beneficial as well. NOW Huperzine A is standardized to 0.1% trituration on Calcium Carbonate.

**Vendor(s):** Wilke Resources **Vendor's Code:** N/A

**Quantity:** pending per drum/case

**Color/Appearance:** A White or slight yellow crystalline free flowing needle-like crystalline powder.

**Taste/Odor:** slight bitter taste, no odor

**Mesh Size:** NLT 100% through # 80 US Standard sieve, NLT 95% through #100 US Standard sieve.

**Powder Density:** ***Tap (Pack):*** 0.779 – 0.861g/ml ***Untap (Loose/Bulk):*** 0.437 – 0.483g/ml

**Assay:** 98.0%- 102.0% purified HupA from extract (Standardized to NLT 0.1% trituration on Calcium Carbonate)

**Specific Gravity (@ 25°C, w/w):** N/A **Optical rotation ($[\alpha]_D$ @24.5°C):** -150.4° (c=0.498 in MeOH)

**pH:** pending **UV Absorbance ($\lambda_{max}$):** 231nm, 313nm (ethanol)

**Refractive Index (@ 20°C, $n_D$):** N/A **Melting point:** 227 – 231°C (also reported at 214-215°C)

**Flash point (Open/Closed cup):** N/A **Infrared Adsorption:** ___% at ___ (pending)

**Freezing point (10% aqu. Soln., w/w):** N/A (solid) **Boiling point (@ 760mm Hg):** N/A (solid)

**Solubility:** ***Water:*** pending ***Alcohol:*** pending ***Acetone:*** pending ***Other:*** pending

# Item # 52400

**Product Class: 995**

**Solvent Used:** ***For Extraction:*** pending ***For Wash:*** N/A
**Solvent Residue:** pending **Sterilization Residue:** pending
**Sterilization Method:** N/Av **Processing:** ***Bleaching:*** N/A ***Bromating:*** N/A

**Ash (Residue on Ignition):** pending **Moisture (Loss on drying)):** NMT 5.0%

**Expiration Date (from time of Mfg.)/ Shelf Life:** (pending) Chemical stability of HupA is excellent. It is resistant to structural changes at different temperatures when placed in acidic or alkaline solutions, thus indicating that HupA will persist longer in the body, and that tablets or capsules will have a longer shelf life. The terminal half-life of Hup A is 4.8 hours. ***Test Method for Shelf Life:*** pending

**Storage:** Store in a cool, dry, and dark environment in a tightly sealed original container.
**Temperature for Storage:** pending **Moisture Free:** Y (very hygroscopic material) **Low Oxygen:** pending

**Maximum Inventory Storage (Weeks):**
**Room Temperature:** Pending **Refrigeration:** Pending **Freezer:** Pending
**Retail Storage Temperature:** Temp. pending

**Packaging – Special Requirements (Inserts):** 4 x 4oz Desiccants for bulk. Incompatible with strong oxidizing agents.

**Specifications- Ingredients by Reference Number, Weight per level teaspoon:**

| Ref. | Weight/ Tspn | Ingredients |
|---|---|---|
| 52400 | 2250-2300mg/tspn | Huperzine A° (0.1% trituration on $CaCO_3$) powder (Wilke Resources) |

**Impurities (maximum permitted levels):**
***Chemical By-Products/ Deterioration Products:*** Not Known ***Pesticides:*** None ***Alkaloid Impurities:*** Absent

**Microbiological / Heavy Metals:** Standard Plate Count: < 100,000/g; Yeast and Molds: < 2,000/g; Coliform: < 300/g; E. coli & Salmonella: Negative
**Heavy Metals:** HM as Lead (Pb): <10ppm; Lead: <5ppm; Arsenic/ Cadmium/ Mercury/Aluminum: <1ppm (each)

All bulk powder ingredients are GMO free (Not genetically engineered)– if available, Non-High Energy Processed (a.k.a. irradiation, Microwaving), contain no artificial flavors or colors, and are preservative free. Only solvents or Manufacturing aids approved by NOW Foods may be used in its production.

**Toxicity:** $LD_{50}$ in rats (ml/kg): 4.6 orally. Hup A is safe because it would take more than 20 times the therapeutic dose (0.2mg/kg, oral) to reach the $LD_{50}$.

**NOW QC Product Tests:** BT, ME, HM, AS, RI, OR, SO, CO, PH, MP, PT

**Assay Method (active ingredient (s)):** HPLC for Huperzine A

**Approved Labs:** American Analytical / Industrial / NOW Foods/ Plant Bioactives

**Distribution Rights (per Legal Counsel):** No restrictions (pending)

**Date Issued:** 10-14-99 **Supersedes:** None **Approved:** Jim Roza
Nilesh Patel

° Pregnant women, and people with hypertension and pulmonary problems should not take it.

# WENLING PHARMACEUTICAL FACTORY

## CERTFICATE OF ANALYSIS

| | | | |
|---|---|---|---|
| Sample name | Huperzine A | Quantity | 1g |
| Packing | Plastic bottle | Batch size | 250g |
| Deliverer | Plant-extra.workshop | Manufacturer | Wenling pharm factory |
| Batch No | 990710 | Rec date | 99.07.10 |
| Criterion | WS-127(X107)-94 | Rep.date | 99.07.13 |

### RESULT

1. Characteristics:
   A white needle-like crystalline powder,odorless,hydroscopic.
2. Melting point:
   228.0~229.0℃ (should be 227~231 ℃)
3. Identification:
   (1) λ max: 231nm, 313nm
   (2),(3) positive
4. Loss on drying:
   2.7% (not more than 5.0%)
5. Related substances:
   Alkaloid impurities I in accord
   Alkaloid impurities II in accord
   Other impurities in accord
6. Assay:
   99.3% (should be 98.0~102.0%)

Conclusion:
This batch of product is conformity with the above criterion.

UV absorbance

Insp. Manager: Chen Jianlong Tester: Chen Yaping

# HUPERZINE A

## TYPICAL CERTIFICATE OF ANALYSIS

| | | | |
|---|---|---|---|
| **Sample Name** | Huperzine A | **Quantity** | 0.3 g |
| **Packing** | Plastic Bottle | **Batch Size** | 350 g |
| **Batch No.** | 9711-01 | **Receiving Date** | 11/3/97 |
| **Criteria** | WS-127(X107)-94 | **Reporting Date** | 11/10/97 |

## RESULTS

| Analysis | Specification | Actual |
|---|---|---|
| 1. Characteristics | White needle-like crystalline powder, odorless & hydroscopic | |
| 2. Melting Point | 227 to 231 °C | 228.5 - 229.5 °C |
| 3. Identification | (1) $\lambda_{max}$: 231 nm, 313 nm | Conforms |
| | (2), (3) positive | |
| 4. Loss on Drying | 5.0% Max. | 1.21% |
| 5. Assay | 98.0 - 102.0% | 101.3% |

**Conclusion:** This batch of product is in conformity with the above criterion.

**Insp. Manager:** _____ **Checker:** _____ **Tester:** _____

[Note: The Certificate of Analysis that accompanies the actual shipment of product will have the seal of the pharmaceutical manufacturer on it]