



DEPARTMENT OF HEALTH & HUMAN SERVICES

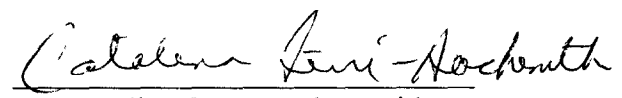
Public Health Service
Food and Drug Administration

Memorandum

Date: March 2, 2003 0861 '03 MAR -3 P1:50
From: Division of Dietary Supplement Programs and Compliance, HFS-810
Subject: 75-Day Premarket Notification of New Dietary Ingredients
To: Dockets Management Branch, HFA-305

New Dietary Ingredient: Idebenone
Firm: Threshold Enterprises Ltd.
Date Received by FDA: December 2, 2002
90-Day Date: March 2, 2003

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 new dietary ingredient 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.


Catalina Ferre-Hockensmith

Attachments

95S-0316

RPT 158



FEB 14 2003

0862 '03 MAR -3 P1:50

Mr. Barry Sugarman, B.S. ENGR.
Consultant to the President
Threshold Enterprises Ltd.
Quality Control Department
11 Janis Way
Scotts Valley, California 95066

Dear Mr. Sugarman:

This letter is in response to your submission to the Food and Drug Administration (FDA), dated November 26, 2002, (as supplemented by information you provided by telefax on December 17, 2002) for a new dietary ingredient made pursuant to 21 U.S.C. 350b(a)(2) (section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)) and 21 CFR 190.6. Your letter notified FDA of your intent to market Idebenone, a substance that you assert is a new dietary ingredient.

The term "dietary supplement" is defined in the Act, as amended by the Dietary Supplement Health and Education Act of 1994, as a product (other than tobacco) intended to supplement the diet that bears or contains a vitamin, a mineral, a herb or other botanical, an amino acid, a dietary substance for use by man to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, extract, or combination of any of the above ingredients (21 U.S.C. 321(ff)(1)). Moreover, to be a dietary supplement, a product must be intended for ingestion in a form described in 21 U.S.C. 350(c)(1)(B)(i) or comply with 21 U.S.C. 350(c)(1)(B)(ii), must not be represented as conventional food or as a sole item of a meal or the diet, and must be labeled as a dietary supplement (21 U.S.C. 321(ff)(2)). The definition excludes an article that is authorized for investigation as a new drug, antibiotic, or biological for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public, which was not before such authorization, marketed as a dietary supplement or as a food (21 U.S.C. 321(ff)(3)(B)).

FDA has carefully considered the information in your submission, and we have concluded that Idebenone is not a dietary supplement because it does not meet the statutory definition of a dietary supplement in 21 U.S.C. 321(ff). First, Idebenone is not a "dietary ingredient" as defined in 21 U.S.C. 321(ff)(1). Second, Idebenone is excluded from the definition of a "dietary supplement" under 21 U.S.C. 321(ff)(3)(B).

Your new dietary ingredient notification is for Idebenone. Idebenone is not a vitamin, mineral, herb or other botanical, amino acid, dietary substance for use by man to supplement the diet by increasing the total dietary intake, or a concentrate, metabolite, constituent, extract

Page 2 – Mr. Barry Sugarman, B.S.ENGR.

or combination of any ingredient described above. Idebenone is also not a “dietary substance” because it cannot reasonably be viewed as a substance “for use by man to supplement the diet by increasing the total dietary intake.” Idebenone is a synthetic analog of coenzyme Q10 that is not food, nor is it used for food. Therefore, Idebenone is not a dietary ingredient.

Furthermore, your product is excluded from the definition of “dietary supplement” under 21 U.S.C. 321(ff)(3)(B). Idebenone is an article authorized for investigation as a drug for which substantial clinical investigations have been instituted in the United States, and the investigations have been made public, and which was not before such authorization marketed as a dietary supplement or as a food.

In sum, the ingredient for which you have submitted a new dietary ingredient notification is not a dietary ingredient under the Act. Moreover, the product to which you refer in your submission appears to be a drug under the Act and thus subject to the regulatory requirements of drugs.

Your submission will be kept confidential for 90 days from the date of receipt, and after April 17, 2003, 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 yours,

A handwritten signature in black ink, appearing to read "Susan Walker", written in a cursive style.

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



THRESHOLD
ENTERPRISES LTD.

Quality Control Department, 11 Janis Way
Scotts Valley, CA 95066
Phone: 831-461-6413
FAX: 831-461-1024

0863 '03 MAR -3 P1:56

December 17, 2002

Catalina Ferre-Hockensmith, Consumer Safety Officer
Office of Nutritional Products, Labeling and Dietary Supplements (HFD-820)
Center for Food Safety and Applied Nutrition, Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740
Phone: 301-436-2371, Fax: 301-436-2636, 2639

Dear Ms. Ferre-Hockensmith,

This acknowledges receipt of your voice mail message dated Friday 12/13/2002 regarding our 75-day notice dated November 26, 2002 for Idebenone. I received the correct spelling of your name and title just this morning when I spoke to your receptionist.

Here is the information that you requested:

Your question: Is this product a tablet or capsule? Our Answer: We intend to manufacture both a tablet and a capsule.

Your question: Are there any target populations that are excluded from use? Our Answer: We will have the same warning that we have on our CoEnzyme Q10 products which is: "Warning: If you are pregnant or breastfeeding, consult your healthcare professional before using this product."

Your question: What strengths will the product be? Our answer: We intend to have a number of strengths between 15 mg and 300 mg per tablet or capsule. The total daily dose will be between 15 mg and 300 mg taken in divided doses 1 to 3 times per day.

Your question: What other ingredients will be present? Our Answer: Tablet and capsule excipients will be used such as microcrystalline cellulose, stearic acid, magnesium stearate, colloidal silicon dioxide, dibasic calcium phosphate, Croscamellose Sodium, or other commonly used binders or tablet lubricants.

Thank you very much.

Sincerely,


Barry Sugarman, B.S. ENGR., Consultant to the President.

(Office Phone: 310-355-6046, FAX 310-454-9592, email: barry@diverstcch.com)

DISTRIBUTION: Don Cleveland, Norm Nelson, Ira Goldberg, Jeri Anderson, Brian Cayton, Nick Momtchiloff



THRESHOLD
ENTERPRISES LTD.

Quality Control Department, 11 Janis Way
Scotts Valley, CA 95066
Phone: 831-461-6413
FAX: 831-461-1024

0864 '03 MAR -3 P1:50

November 26, 2002

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

Dear Sir or Ma'am,

This is a 75-day notice pursuant to 21 CFR 190.6, and 21 USC 350b of the Dietary Supplement Health and Education Act of 1994. Threshold Enterprises Ltd. (Threshold), 11 Janis Way, Scotts Valley, CA 95066 wishes to notify the Food and Drug Administration that Threshold will market a new dietary ingredient Idebenone, a synthetic analog of Coenzyme Q10 (Ubiquinone), a universally accepted and safe dietary supplement. Accordingly, we are submitting this original and two (2) copies of this notification.

The dietary Supplement which contains Idebenone, will consist of a dosage of 15 to 300 mg of Idebenone per day in a tablet or capsule, which will be suggested to be taken one (1) to three (3) times per day in divided doses.

Attached, please find a published review of 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.

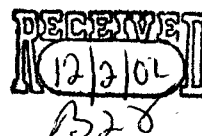
Threshold has contacted Takeda, one of the manufacturers of Idebenone ingredient, and they have advised that this ingredient is not currently the subject of any Investigational New Drug (IND) applications. Further, we have included information indicating that the product is already being offered for sale as a 45 mg per capsule/tablet dietary supplement in the marketplace in the United States by other firms.

Thank you very much.

Sincerely,

Barry Sugarman, B.S. ENGR.
Consultant to the President (Office Phone: 310-355-6046, FAX 310-454-9592, email: barry@diverstech.com)

Enclosures: Chemistry Information and Published Studies



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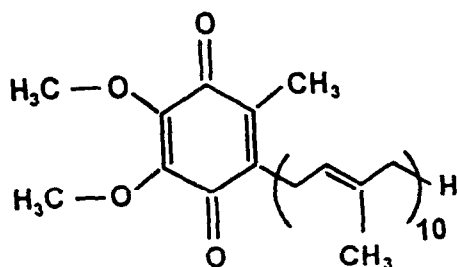


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Scotts Valley, CA 95066
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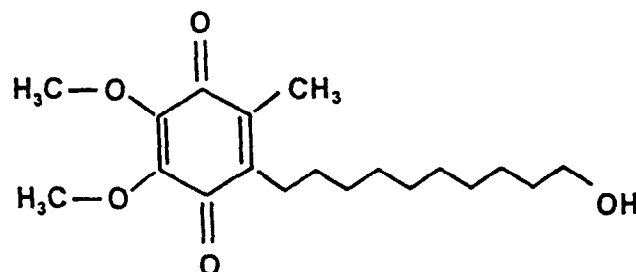
Structural Formulas:

Co-Enzyme Q10



Coenzyme Q-10

Idebenone



QSA-10 (Idebenone)

**Co-Enzyme Q10 (Ubiquinone) is an accepted dietary supplement.
Idebenone is a structural analog to Co-Enzyme Q10**



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Kirkman's Idebenone Hypoallergenic Capsules

[description](#) • [ingredients](#) • [recommended use](#) • [FAQs](#)



Form: Capsules
Package Size: 60 ct.
Product Class: Specialty Product
Primary Use: An analog of Coenzyme Q-10 possessing powerful antioxidant properties

\$25.00
 Now Shipping

[add to cart](#)

| Product | Form | Size | Price | Articles |
|---------------------------------------------|----------|--------|---------|----------|
| Kirkman's Idebenone Hypoallergenic Capsules | Capsules | 60 ct. | \$25.00 | articles |

Ingredients:

| Each capsule supplies | |
|-----------------------|-------|
| Idebenone | 45 mg |

Other Ingredients: Plant Cellulose, Silicon Dioxide, and Magnesium Stearate (Vegetable).

NOTE: Kirkman's Idebenone does not contain any wheat, casein, gluten, sweeteners, corn, yeast, starch, artificial colors or flavors.

Recommended Usage:

As a dietary supplement:

| According to age | Capsules |
|------------------|--------------------|
| Younger Children | 1-2 capsules daily |
| Older Children | 2-4 capsules daily |
| Adults | 2-4 capsules daily |

These statements have not been evaluated by the Food & Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.

[Home](#) | [About Kirkman Labs](#) | [Contact Us](#) |

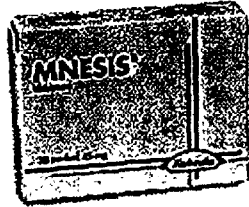
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MNESIS (IDEBENONE)*

Idebenone is a cerebral stimulant and increases brain energy levels. It is also used to treat and prevent strokes. The chemical structure of Idebenone is similar to that of co-enzyme Q10. However researchers believe that

CoQ10 under certain circumstances may become a pro-oxidant, a trait not present in Idebenone. Like CoQ10, Idebenone has protects the heart and is a potent antioxidant.

According to a study published in Neuropsychobiology (1997;36:73-82), "three hundred patients with mild-to-moderate Alzheimer's disease were randomized to receive either placebo, idebenone 30 mg three times per day, or 90 mg three times per day for six months. Statistically significant improvement was noted in the total score of the Alzheimer's Disease Assessment Scale (ADAS-total), and in one cognitive parameter (ADAS-cog). An analysis of therapy responders revealed significant improvement in three outcome measures (clinical global response, ADAS-Cog, and non-cognitive scores) in the idebenone 90 mg three times per day group, compared to placebo".

May cause insomnia, gastralgia, nausea and anxiety. No known contraindications. If taking other anti-convulsants, consult a Doctor before beginning this medication.

\$49.00 size/dose:

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Home Product info To Order IAS Ltd.

| BRAIN PRODUCTS | | wholesale prices bottom of page | | |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|---------------------------------|----------|--------------|
| Order | Acetyl L-Carnitine 12 bottles @ \$15 | 500 mg | 50 caps | 24.95 |
| Order | Attention! | 482 mg | 90 caps | 14.95 |
| Order | CDP Choline | 200 mg | 60 caps | 19.95 |
| Order | DMAE veggie caps | 250 mg | 100 caps | 9.95 |
| Order | Galantamine www.galantamine.cc | 8 mg | 60 caps | 39.95 |
| Order | GalantaMind™ 8mg galantamine, 200mg choline, 100mg Vit B-5 | 8 mg | 30 caps | 29.95 |
| out of stock | GalantaMind™ | 8 mg | 90 caps | 69.95 |
| Order | Ginkgo Biloba 24% | 60 mg | 60 caps | 4.95 |
| Order | Huperzine A | 50 mcg | 120 caps | 19.95 |
| Order | Idebenone www.idebenone.info | 45 mg | 30 caps | 29.95 |
| Order | NADH Enada | 5 mg | 30 tabs | 19.95 |
| Order | Phosphatidylserine | 100 mg | 60 caps | 29.95 |
| Order | Picamilon www.picamilon.net | 100 mg | 60 caps | 27.95 |
| Order | Pyritinol www.pyritinol.info | 200 mg | 60 caps | 29.95 |
| Order | Pyroglutamic Acid | 1000 mg | 120 tabs | 23.95 |
| Order | Vinpocetine www.vinpocetine.info | 20 mg | 60 caps | 19.95 |
| Order | Vinpocetine 12 bottles @ \$12 = \$144 | 20 mg | 720 caps | \$144 |
| Order | Get Smart™ | 313 mg | 60 caps | 34.95 |
| Order | Get Smart™ 12 bottles @ \$21 = \$252 | 313 mg | 720 caps | \$252 |
| ingredients: vinpocetine 10mg, Huperzine A 100mcg, DMAE 75mg, pyritinol 100mg, bacopin 50mg, ginkgo biloba 25mg, galantamine 350mcg, Idebenone 3mg, Rhodiola rosea 50mg | | | | |
| Order | Pay Attention™ 12 bottles @ \$15 | 232 mg | 60 caps | 24.95 |
| ingredients: vinpocetine 5mg, Huperzine A 75mcg, DMAE 75mg, pyritinol 25mg, bacopin 50mg, ginkgo biloba 25mg, galantamine 100mcg, Idebenone 2mg, Rhodiola rosea 33mg | | | | |
| Order | MegaMind™ | | 30 tabs | 15.95 |
| Order | MegaMind™ | | 60 tabs | 25.95 |
| ANTIOXIDANTS | | | | |
| Order | Alpha Lipoic Acid | 300 mg | 60 caps | 19.95 |
| Order | Alpha Lipoic Acid 12 bottles @ \$12 | 300 mg | 720 caps | \$144 |
| Order | Carnosine buy 2 get 1 free | 100 mg | 60 caps | 19.95 |
| Order | Carnosine 12 bottles @ \$10 | 100 mg | 720 caps | \$120 |

| | | | | |
|----------------------------------------------------------------------------------|---------------------------------------------------------------------------------|---------|-----------|--------------|
| Order | Carnosine eye drops | | 5 x 2 ML | 34.00 |
| Carnosine article #1 Carnosine article #2 Carnosine eyedrops article | | | | |
| Order | Coenzyme Q10 each cap also contains 10mg idebenone | 100 mg | 60 caps | 29.95 |
| Order | Coenzyme Q10 12 bottles @ \$20 each cap also contains 10mg idebenone | 100 mg | 720 caps | \$240 |
| Order | Coenzyme Q10 in rice bran oil | 100 mg | 50 gels | 29.95 |
| Order | Germanium Ge-132 | 100 mg | 30 caps | 19.95 |
| Order | Grape Seed | 60 mg | 90 caps | 10.95 |
| Order | Green Tea | 400 mg | 100 caps | 9.95 |
| Order | Idebenone www.idebenone.org | 45 mg | 30 caps | 29.95 |
| Order | Life Extension Mix™ | | 490 caps | 69.95 |
| Order | Lutein | 20 mg | 60 caps | 14.95 |
| Order | Lycopene | 10 mg | 60 gels | 19.95 |
| Order | N-Acetyl Cysteine | 600 mg | 100 caps | 17.95 |
| | PBN alpha phenyl t-butyl nitron | 30 mg | 30 caps | 30.00 |
| Order | Quercetin | 400 mg | 120 caps | 19.95 |
| Order | Super Antioxidants™ | 470 mg | 60 caps | 14.95 |
| Order | Tocotrienols | 150 mg | 60 caps | 19.95 |
| Order | Vinpocetine | 20 mg | 60 caps | 19.95 |
| HORMONES | | | | |
| Order | Androstenedione + diol | 200 mg | 60 caps | 19.95 |
| Order | DHEA | 50 mg | 50 caps | 9.95 |
| Order | DHEA | 100 mg | 50 caps | 14.95 |
| Order | DHEA 7-Keto | 25 mg | 90 caps | 19.95 |
| Order | Melatonin sublingual | 3 mg | 90 tabs | 6.95 |
| Order | Pregnenolone | 50 mg | 60 caps | 12.95 |
| MISC. | | | | |
| Order | Adrenal bovine adrenal cortex extract | liquid | 15 ML | 36.00 |
| Order | ATP enteric coated tablets | 60 mg | 60 tabs | 15.95 |
| Order | Glucosol™ regulates blood sugar | 24 mg | 60 gels | 13.95 |
| Order | Ipriflavone | 200 mg | 60 caps | 6.95 |
| Order | PRO hGH take 2 tabs 5 days on 2 days off | | 40 tabs | 99.95 |
| Order | SAMe blister packed | 20 mg | 20 tabs | 19.95 |
| Order | Saw Palmetto | 160 mg | 60 gels | 8.95 |
| Order | Serrapeptase | 5 mg | 120 tabs | 17.95 |
| Order | Serrapeptase 12 bottles @ \$10 | 5 mg | 1440 tabs | \$120 |
| serrapeptase studies serrapeptase testimonials serrapeptase references | | | | |
| Order | Testasomal™ transdermal cream 5000mg androstenedione + androstenediol | 5000 mg | 2 oz | 19.95 |

| | | | | |
|-----------------------|----------------------------------------------|--------|----------|--------------|
| Order | Theanine green tea extract - relaxant | 100 mg | 90 caps | 19.95 |
| Order | 5-Hydroxy Tryptophan | 50 mg | 60 caps | 14.95 |
| IMMUNE SUPPORT | | | | |
| Order | Beta-1,3/1,6-Glucan | 100 mg | 90 caps | 19.95 |
| Order | Cetyl Myristoleate | 100 mg | 180 gels | 59.95 |
| Order | Germanium Ge-132 | 100 mg | 30 caps | 19.95 |
| Order | Germanium Ge-132 12 bottles @ \$12 | 100 mg | 360 caps | \$144 |
| Order | IP-6 | 800 mg | 100 caps | 21.95 |
| Order | Monolaurin | 500 mg | 100 caps | 19.95 |
| Order | Olive Leaf 10% | 500 mg | 60 caps | 14.95 |
| Order | Oregano Oil | | 90 gels | 14.95 |
| Order | Tea Tree Oil | | 1 oz | 8.95 |

Quantity Discounts

| | | | | | |
|-------|--------------------------------------------------------------|--------|----------|--------------|----------------|
| Order | Acetyl L-Carnitine | 500 mg | 50 caps | 12 bottles @ | \$15.00 |
| Order | Alpha Lipoic Acid | 300 mg | 60 caps | 12 bottles @ | 12.00 |
| Order | Cardio Chelate 400mg EDTA | 650 mg | 60 caps | 12 bottles @ | 12.00 |
| Order | Cardio Chelate 400mg EDTA | 650 mg | 180 caps | 12 bottles @ | 24.00 |
| Order | Carnosine | 100 mg | 60 caps | 12 bottles @ | 10.00 |
| Order | Coenzyme Q10 each cap also contains 10mg idebenone | 100 mg | 60 caps | 12 bottles @ | 20.00 |
| Order | Galantamine | 8 mg | 60 caps | 12 bottles @ | 24.00 |
| Order | Germanium Ge-132 | 100 mg | 30 caps | 12 bottles @ | 12.00 |
| Order | Get Smart™ | 313 mg | 60 caps | 12 bottles @ | 21.00 |
| Order | Idebenone www.idebenone.org | 45 mg | 30 caps | 12 bottles @ | 20.00 |
| Order | Monolaurin | 500 mg | 100 caps | 12 bottles @ | 12.00 |
| Order | Pay Attention™ | 232 mg | 60 caps | 12 bottles @ | 15.00 |
| Order | Phosphatidylserine | 100 mg | 60 caps | 12 bottles @ | 22.00 |
| Order | Pyritinol www.pyritinol.org | 200 mg | 60 caps | 12 bottles @ | 18.00 |
| Order | Serrapeptase 10,000 units/ tab | 5 mg | 120 tabs | 12 bottles @ | 10.00 |
| Order | Vigorex | | 60 caps | 12 bottles @ | 15.00 |
| Order | Vinpocetine veggie caps | 20 mg | 60 caps | 12 bottles @ | 12.00 |
| Order | 5-Hydroxy Tryptophan | 50 mg | 60 caps | 12 bottles @ | 7.50 |

Quantity Discounts

Smart Nutrition
1765 Garnet Ave #66
San Diego, CA 92109

we sell picamilon, vinpocetine, carnosine, monolaurin, serrapeptase, idebenone, pyritinol.

Page 4 of 4

phone: 800-599-8607
phone: 858-270-9015
fax: 802-609-5932
smart@smart-nutrition.net

3819