

ORIGINAL

**Syntech (SSPF)
International, Inc.**

SEP 24 2004
A.B./FDA

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

Premarket Notification for a New Dietary
Ingredient: Betaphrine

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Submitted by:

Bo Zhu

President

Syntech (SSPF) International, Inc.

310 Paseo Tesoro

Walnut, CA 91789

Tel: 909.444.5888

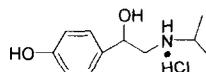
Syntech (SSPF) International, Inc.

Premarket Notification for a New Dietary Ingredient: Betaphrine

Material

1. Nature of the material

- a. Product name: Betaphrine™
- b. Chemical Names:
dl-1-(4-hydroxyphenyl)-2-isopropylaminoethanol hydrochloride
Isopropyloctopamine hydrochloride
- c. CAS Number: 7376-66-1
- d. Molecular formula: $C_{11}H_{18}ClNO_2$
- e. Molecular Weight: 231.5
- f. Melting Point: 153.5°C
- g. Molecular Structure:



2. Origination

Betaphrine is a derivative of the natural substance octopamine.

3. Derivation

- a. Semi-synthesis from the natural substance octopamine:



- b. Total synthesis from phenol.

Presentation

1. Betaphrine is intended for inclusion in dietary supplements for the purpose of supporting the maintenance of normal weight.
2. Recommended intake:
 - a. Supplements contain between 20 mg and 80 mg of Betaphrine per serving.
 - b. Supplements containing Betaphrine are consumed between one and three times per day.
 - c. The maximum daily-recommended consumption is 80 mg per day.

Safety Information

In accordance with Title 21 United States Code of Federal Regulations (21CFR) Section 190.6, the following information is provided to show the basis on which we conclude there is a reasonable expectation of the safety of Betaphrine when used under the conditions and recommendations suggested in the labeling of dietary supplements containing Betaphrine.

The study of Betaphrine and similar substances demonstrates the following:

Human data involving the consumption of Betaphrine in orally administered levels at a maximum level of 80 mg Betaphrine.ⁱ

The demonstrable LD50 of Betaphrine in mice is shown as 370 mg/kg i.p. and 144 mg/kg i.v.ⁱⁱ

Recognizing that Betaphrine is intended to be marketed in the "weight-loss" segment of the Dietary Supplement Industry, it is important to note distinctions between Betaphrine and other ingredients that used in this market segment. This additionally supports our reasonable basis for safety. The Food and Drug Administration has banned the used of ephedra alkaloids in dietary supplements (inclusive of those intended for weight-loss applications) owing to its adverse effects on blood pressure. Betaphrine demonstrates no such effect on blood pressure as evidenced in the previously cited human study and in a rabbit model.ⁱⁱⁱ Moreover, data indicate that in the human, Betaphrine does not elevate blood pressure even when infused at a rate of 0.5 mg/min to a total of 15 mg.^{iv}

The recommended maximum consumption of Betaphrine in dietary supplements is at 80 mg per day owing to the nature of the data included in the notification. There is evidence found in the studies that consumption of extremely elevated levels of Betaphrine (the equivalent of 2.5 times the recommended serving for Betaphrine) showed a lowering of blood pressure. For this reason the labeling of supplements containing Betaphrine shall include the following cautionary language:

Persons with hypotension (low blood pressure) or who have had a history of low blood pressure should not consume this product. Not for pregnant or lactating women. Not for use by children.

The first portion of the language proposed for inclusion is in direct address of the data found in used in support our demonstration of the safety of Betaphrine. The second portion of the language is owed to there being no current evidence of Betaphrine having been used in pregnant or lactating women. The third part of the language shown is a reflection of the lack of evidence that children have consumed this specific dietary ingredient.

Referenced articles are cited at the conclusion of this notification and copies of the reprints of these articles are included with the notification in accordance with 21CFR §190.6(b)(4).

Discussion

The presentation of Betaphrine in dietary supplements is intended to provide the consumer with the opportunity to supplement their diet with the ingredient isopropyloctopamine.

In accordance with the Section 201(ff) for the Federal Food, Drug and Cosmetic Act (FFDCA), Betaphrine is a dietary ingredient in that it is:

A product (other than tobacco) that is intended to supplement the diet . . ."

Supplements containing Betaphrine further meet the statutory definition in that they contain:

. . . a dietary substance for use by man to supplement the diet by increasing the total daily intake, or concentrate, metabolite, constituent, extract or combination of these ingredients."

In accordance with the statutory requirements of Section 413(a) of FFDCA (Title 21 United States Code Section 350b(a)) Betaphrine is a New Dietary Ingredient in that it is a substance that has not been used in dietary supplements for sale in the United States to this date.

The consumption of Betaphrine is specifically intended as a supplement to the diet for the purpose of helping to maintain normal weight.

Owing to Betaphrine meeting the requirements of Section 201(ff) of FFDCA and its further meeting the requirements for notification as found in Section 413(a) of FFDCA, this notification is submitted applying the requirements set forth in 21CFR §190.6.

As a foundation for our determination that there is a reasonable basis to find Betaphrine safe when consumed at the suggested use level we refer to the consumption of octopamine as a compound found in foods. The consumption of octopamine occurs typically with the consumption of plants and plant extracts that contain the compound (notably *Citrus aurantium*). There is no current evidence that such consumption of octopamine is unsafe. Since Betaphrine is a derivative of octopamine, it is chemically altered relative to the form in which it is found in foods and thus further meets the criteria for a New Dietary Ingredient as cited in Section 413(a)(2) of FFCA.

The citations included with this notice indicate the safe use of Betaphrine when consumed at the levels recommended. The evidence provided is specific to Betaphrine. Moreover, included in this notification is the assertion that a cautionary be included in the labeling of each package of dietary supplement containing Betaphrine. The proposed inclusion of such language recognizes the totality of the information we used in our determination of the safety of Betaphrine. Any structure/function claims associated with the labeling of product containing Betaphrine will be notified in accordance with 21CFR §101.90.

Conclusion

This notification is submitted as required by statute and reports the evidence upon which made the determination that Betaphrine will reasonably expected to be safe when consumed in dietary supplements at the recommended levels of consumption.

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- ⁱ Marsh DF; *Arch. Int. Pharmacodyn.*; 1949, 78(3), pp 489-498.
 - ⁱⁱ Lands AM; *J. Pharmacol. Exptl. Therap.* 1952, 106, pp 341-345.
 - ⁱⁱⁱ Muhlbachova E; *Physiologia Bohemoslovaca*, 1973, 22, pp 503-512.
 - ^{iv} Pilkington TRE; *J. Lipid Res.*, 1966, 7, pp 73-76.

Respectfully Submitted

Bo Zhu



9/17/04

President
Syntech (SSPF) International, Inc.