



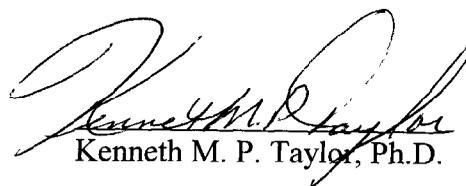
Memorandum

Date: January 16, 2003
From: Chemist, Division of Standards and Labeling Regulations, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-821
Subject: 75-Day Premarket Notification of New Dietary Ingredients
To: Dockets Management Branch, HFA-305

0429 '03 JAN 27 P2:21

Subject of the Notification: N-acetylserotonin (Normelatonin)
Firm: Heartmind Nutrition
Date Received by FDA: July 26, 2002
90-Day Date: October 24, 2002

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 substance 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.


Kenneth M. P. Taylor, Ph.D.

Attachments

95S-0316

RPT 146



OCT - 4 2002

Mr. Clayton A. Prepsky
Heartmind Nutrition
1015 North 2nd Avenue
435 B
Phoenix, Arizona 85003

Dear Mr. Prepsky:

This is in response to your submission of a new dietary ingredient notification, dated July 21, 2002, to the Food and Drug Administration (FDA) pursuant to 21 U.S.C. 350b(a)(2) and 21 Code of Federal Regulations (CFR) Part 190.6. FDA received your notification on July 26, 2002, of your intent to market a product containing the ingredient N-acetylserotonin (normelatonin) from a botanical source.

In accordance with 21 U.S.C. 350b(a)(2), the manufacturer or distributor of a dietary supplement that contains a new dietary ingredient that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered must submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into 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 21 U.S.C. 350b(a)(2), there must be a history of use or other evidence of safety establishing that the new 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.

Your submission indicates that you intend to market N-acetylserotonin as a tablet containing 1 mg of the ingredient with a recommended serving of 1 to 2 tablets taken at bedtime. You also intend on marketing a second related product containing 2 mg N-acetylserotonin with 100 mg alpha/gamma tocopherol. You indicate that a 2 mg portion of this product is to be taken once daily at bedtime.

FDA has carefully considered the information in your submission, and the agency has significant concerns about the evidence on which you rely to support your conclusion that

dietary supplements containing N-acetylserotonin, when used under the conditions recommended or suggested, will reasonably be expected to be safe. You state in your submission that “Millions of people have consumed melatonin as a dietary supplement over the last ten years in dosages from 1-20 mg. The recommended dosage of 1-2 mg N-acetylserotonin is based on the approximate quantities of exposure thousand of consumers have had to this antioxidant, as a metabolite of 9-20 mg of melatonin supplementation. The dosage is also based on the theoretical formation of 1-2 mg of melatonin from the formation of 1-2 mg of N-acetylserotonin.” However, your notification contains no information to support these statements nor establishes that historical use, if any, is relevant to reaching a conclusion that your product when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. Your submission contains twenty-five reference articles, the majority of which focus on melatonin and N-acetylserotonin metabolism. You indicate that N-acetylserotonin was administered to healthy human males in doses of 25, 50 and 75 mg in reference 3. However, the reference provided is incomplete as only the abstract is provided. You also state, in your notification, that N-acetylserotonin was administered to human subjects in 75 mg doses for 90 days with no adverse responses but you provide no documentation to support this assertion. Studies that document use of melatonin, which you include, do not establish evidence of safety for the N-acetylserotonin, which is the subject of your notification. Furthermore, you stated in your submission that you relied on a rat study in which L-5-hydroxytryptophan, not N-acetylserotonin, was used to induce serotonin syndrome. However, you did not describe the relevance of this study to N-acetylserotonin and how it establishes safety of the new dietary ingredient.

Furthermore, your notification is incomplete because it does not comply with 21 CFR 190.6 (copy enclosed). (You may view FDA’s web site at <http://www.cfsan.fda.gov/~dms/ds-ingrd.html> for additional details on new dietary ingredient notification requirements.) For example, your notification:

- Does not include the Latin binomial name (stating the author) of the herb or botanical [21 CFR 190.6 (b)(2)].
- Does not indicate the intended form of ingestion of the N-acetylserotonin/tocopherol mixture and FDA is unable to determine the form of the supplement from the information supplied [(21 CFR 190.6 (3)(ii) and 321 U.S.C. (ff)].

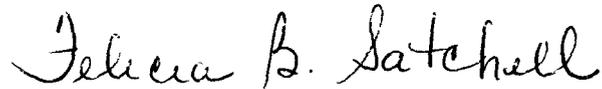
For the reasons discussed above, the information in your submission does not provide an adequate basis for safety to conclude that N-acetylserotonin, when used under the conditions recommended or suggested, will reasonably be expected to be safe. Therefore, your product may be adulterated under 21 U.S.C. 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 by 21 U.S.C. 331 (a) and (v).

Page 3 – Mr. Clayton A. Prepsky

Your notification will be kept confidential for 90 days after the filing date. After October 24, 2002, the notification and related correspondence from FDA will be placed on public display at FDA's Dockets Management Branch in docket number 95S-0316. However, any trade secret or otherwise confidential commercial information that is in the notification will not be disclosed to the public.

If you have any questions concerning this letter, please contact me at (301) 436-2371.

Sincerely yours,



Felicia B. Satchell
Director
Division of Standards
and Labeling Regulations
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

Enclosure

Premarket Notification: Normelatonin (N-acetylserotonin)
New Dietary Ingredient

July 21, 2002

Division of Standards and Labeling Regulations
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, 20740-3835

Dear Sir or Madam:

Pursuant to Section 8 of The Dietary Supplement Health and Education Act 1994, Heartmind Nutrition wishes to inform the FDA of our intention to manufacture and distribute N-acetylserotonin (normelatonin) as a new dietary ingredient in a dietary supplement to promote human health. N-acetylserotonin (normelatonin) is a metabolite of melatonin, a dietary ingredient on the market before October 15, 1994.

Heartmind Nutrition has used due diligence in evaluating the potential health benefits and any possible health risks in the use of N-acetylserotonin (normelatonin) as a new dietary ingredient. All available information forms the basis for our conclusion that the use of N-acetylserotonin (normelatonin) is reasonably expected to be safe in the dosages recommended on the label.

Heartmind Nutrition has developed a method for producing 99.9% pure N-acetylserotonin (normelatonin) from a botanical source under non-microbial conditions. The contract manufacture will only use a GMP facility.

N-acetylserotonin (normelatonin) will be marketed in 1mg dosages as a tablet. The recommended dosage is 1 to 2mg at bedtime as an antioxidant. A Heartmind Nutrition product containing 2mg N-acetylserotonin (normelatonin) as a dietary ingredient in a dietary supplement containing 100mg alpha/gamma tocopherol mixture will also be marketed. The dietary supplement containing normelatonin 2mg as a dietary ingredient is to be taken once daily at bedtime.

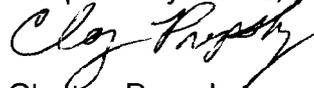
The label will have a warning:

"Take this product only at bedtime. If you are taking prescription medication consult with your physician before taking any dietary supplement. Do not take this product if you have been diagnosed with low blood pressure, are pregnant or breast feeding, or are diagnosed with depression. This product is not intended to treat, cure, prevent, or mitigate disease. "

Your time and attention in the evaluation of this notification is greatly appreciated. If you have any questions concerning the manufacturing procedures developed by Heartmind Nutrition we would be pleased to provide additional information. We would request such information be kept confidential, as it is a proprietary process.

Phone (602-795-6348)
Contact: Clayton A. Prepsky

Respectfully Yours,


Clayton Prepsky

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Background on N-acetylserotonin (Normelatonin)

N-acetylserotonin is the biosynthetic precursor and a hepatic metabolite of the natural substance melatonin. N-Acetylserotonin may also be referred to as normelatonin (Lezoualc'h et al.1998 ref. 1.) (Sigma specification ref. 22). Melatonin (N-acetyl-O-methylserotonin) is a dietary ingredient on the market before October 15, 1994. Melatonin is consumed in the diet and has been detected in bananas, rice, and cherries (Reiter 2001 ref. 2.).

Oral administration of N-acetylserotonin in humans increases N-acetyl-O-methylserotonin (melatonin) production in a dose dependent manner (Shteinlukht et al.1998 ref.3). Dietary supplementation with normelatonin to maintain physiological levels of melatonin would be an effective way to balance the total antioxidant status of the blood (Reiter et al.1999 ref. 4.). The potential health benefits of N-acetylserotonin (normelatonin) as a new dietary ingredient are not limited to its role as the biosynthetic precursor of melatonin. N-acetylserotonin is a potent antioxidant independent of its conversion to melatonin in the body. N-acetylserotonin is neuroprotective in human neurons (ref.1.) and is 10x more potent than melatonin in protecting human low density lipoprotein (LDL) from free radical mediated oxidation (Seeger et al. 1997 ref. 5.) Serum levels of N-acetylserotonin are 10-100 times higher than melatonin in humans (Wolfer et al.1999 ref.6.).

Normelatonin History of Use:

- 1. N-Acetylserotonin (Normelatonin) is a metabolite of melatonin supplementation.***
- 2. Oral N-acetylserotonin (Normelatonin) supplementation increases melatonin formation in healthy humans.***

Reasonable expectation of safety for recommended dosage 1-2 mg N-acetylserotonin:

- 1. N-Acetylserotonin 1-2mg orally as an antioxidant before bedtime correlates to quantities of long term human exposure to N-acetylserotonin (Normelatonin) as hepatic metabolite of exogenous melatonin in healthy humans.***
- 2. Long term oral supplementation with 1mg/kg N-acetylserotonin in animal models (mice) for 22 months resulted in only beneficial effects.***
- 3. L-5-Hydroxytryptophan supplementation increases N-acetylserotonin and melatonin levels***

Melatonin is a ubiquitous molecule first isolated from bovine pineal glands in 1958. In the last two decades an exponential amount of scientific research has elucidated the role of this hormone in maintaining oxidative homeostasis in organisms as diverse as algae and man. In the last decade the distribution of melatonin in a large number of edible plants has been quantified. Ingestion of foodstuffs containing melatonin elevated plasma levels of the hormone in vertebrates (Hattori et al.1995 ref. 7.).

Millions of people have consumed melatonin as a dietary supplement since 1992 in recommended dosages from 1 to 20mg. No significant toxicity or adverse reactions have been reported from the long-term human consumption of melatonin as a dietary supplement. This directly correlates with the increased long-term exposure millions of consumers have had to its metabolite N-acetylserotonin. It is established that the supplemental use of melatonin produces N-acetylserotonin by O-demethylation in the liver.

In man, N-acetylserotonin represents an average 15% of melatonin metabolites formed by exogenous melatonin (Young et al. 1985 ref. 8.). Melatonin is metabolized one way in the liver of humans and another in the central nervous system (Lerner et al. 1978 ref. 19.). The low bioavailability of melatonin supplementation has been explained in terms of a large first pass metabolism (Facciola et al. 2001 ref. 9.). Demuuro et al. (reference 20) report approximately 15% of the oral dosage of melatonin is bioavailable with 2 and 4mg in human volunteers. Approximately 85% is metabolized in first pass metabolism. In human liver there are two principle metabolites N-acetylserotonin and 6-hydroxymelatonin. Human liver microsomes and expressed human cytochrome P-450 convert melatonin to N-acetylserotonin in vitro (ref. 9).

In a typical 10 mg dosage of melatonin as much as 1.5 mg ($\pm 15\%$) of N-acetylserotonin would be formed in the liver from first pass and circulating melatonin. Anecdotally many consumers take several supplements of melatonin sold in 10mg dosages at bedtime. Melatonin is commercially available in 20mg dosages (reference 23). A dosage of 20 mg would correlate to the approximate formation of 3.0 mg ($\pm 15\%$) N-acetylserotonin in human liver. N-acetylserotonin conferred antioxidant protection to rat liver in vivo (Calvo et al. 2001 ref. 10.). N-acetylserotonin maintains membrane fluidity and reduces lipid peroxidation in rat hepatic microsomes (Garcia et al 2001 ref. 21.).

Supplementation with exogenous melatonin increases the hepatic formation of N-acetylserotonin as evidenced by increased urine excretion of sulphate and glucuronide conjugates. Oral administration of 1g melatonin allows the isolation of the metabolic N-acetylserotonin conjugates from human urine (Leone et al. 1987 ref. 11.). Leone et al. were able to isolate 226 mg of NAS (normelatonin) conjugates from the pooled urine of three volunteers who each ingested 1000mg melatonin. Investigations of acute dosages of melatonin 6g orally in humans have shown no clinically significant toxicity (Lerner 1978 ref. 19.) The oral dosage of 6g melatonin correlates with the hepatic formation of approximately 500-900 mg ($\pm 15\%$) N-acetylserotonin.

Oral administration of N-acetylserotonin to healthy human males in dosages of 25, 50, and 75mg increased melatonin levels in a dose dependent manner, as evidenced by urinary excretion of 6-hydroxymelatonin as sulphate conjugates (Sheinlukht et al. 1998 ref. 3.). The substantial production of N-acetylserotonin as a metabolite from dietary supplementation with melatonin and the formation of melatonin from supplementation of moderate doses of N-acetylserotonin (normelatonin) support the reasonable expectation of safety for normelatonin as a new dietary ingredient. No LD-50 for melatonin has ever been established as it one of the safest and least toxic molecules known (Barchas Dacosta et al. 1967 ref. 24). Injections of 800mg/kg in mice failed to produce death.

Millions of people have consumed melatonin as a dietary supplement over the last ten years in dosages from 1-20 mg. The recommended dose of 1-2 mg N-acetylserotonin (normelatonin) is based on the approximate quantities of exposure thousands of consumers have had to this antioxidant, as a metabolite of 9-20 mg of melatonin supplementation. The dosage is also based on the theoretical formation of 1-2 mg of melatonin from the ingestion of 1-2 mg N-acetylserotonin. The molecular weights of N-acetylserotonin and melatonin are 218.26 and 232.3 respectively.

Long term oral administration of N-acetylserotonin in several strains of mice 2.5 mg/kg for up to 22 months further indicates the intrinsic safety of this molecule (Oxenkrug et al. 1999 ref. 13.) in small oral doses. Life span was not significantly increased in female mice. In male C3H mice life span was increased by 20% by N-acetylserotonin 1mg/kg(p.o.) in drinking water. The administration of N-acetylserotonin increased the antioxidant capacity of kidney and brain using in vivo models. Aged animals administered N-acetylserotonin had shiny coats and less balding than animals fed a control diet devoid of this antioxidant. N-acetylserotonin and melatonin independently conferred neuroprotective and cognition enhancing effects against neurotoxins in vivo when administered to rats orally at 1mg/kg and 3mg/kg respectively (Bachurin et al. ref. 12.).

The biosynthesis of serotonin occurs via the tryptophan pathway in humans. Hundreds of thousands of people benefit from the supplemental use of L-5-hydroxytryptophan (5HTP). N-acetylserotonin is formed in vivo by the acetylation of serotonin derived from the decarboxylation of L-5-hydroxytryptophan. The ingestion of this widely used supplement (5-HTP) increases peripheral and cerebral serotonin, and its metabolites N-acetylserotonin and melatonin. Dietary supplementation with 5-HTP increases N-acetylserotonin production and this further demonstrates the safety of small dosages of N-acetylserotonin as a new dietary antioxidant.

Heartmind Nutrition has considered all available information in its determination of a reasonable expectation of safety for N-acetylserotonin as a new dietary ingredient. The scientific literature and premarket consumption continue to support the intrinsic safety of this endogenous antioxidant.

Evaluation of Health Risks:

Acute dosages of 5-HTP produce serotonin syndrome in rats; 75mg normelatonin orally for 90 days resulted in no adverse responses in healthy men and women

Heartmind Nutrition has carefully considered two rat studies, conducted by the same authors, on the pharmacologic regulation of "serum N-acetylserotonin" levels which reported behavioral changes in rats characteristic of the "serotonin syndrome"(Burns et al. 1982 ref. 14.) and (Brown and Burns et al. 1984 Ref.15.). These studies are of questionable relevance to the use of low oral dosages of N-acetylserotonin (normelatonin) as a dietary ingredient in humans. Serum levels of N-acetylserotonin are 10-100 times higher than melatonin in humans (Wolfer et al.1999 ref. 6.).

The experimental design relied on several strategies to manipulate serum N-acetylserotonin levels. Humans and rats produce serotonin by the decarboxylation of L-5-hydroxytryptophan via tryptophan decarboxylase. This enzymatic process is inhibited by the synthetic compound carbidopa. The authors pretreated rats with 100mg/kg carbidopa followed ten minutes later by nialamide. One hour later rats were injected with 28mg/kg L-5-hydroxytryptophan or a synthetic compound N-acetyl-L-5-hydroxytryptophan 33mg/kg. These dosages are equivalent to injection of over a gram of L-5-hydroxytryptophan in humans. The animals were killed thirty minutes later and serum levels of N-acetylserotonin were measured. After injections "rapid" behavioral changes characteristic of the serotonin syndrome were observed. The rat studies injected L-5-hydroxytryptophan not N-acetylserotonin (normelatonin). Most importantly, "serotonin syndrome" is not a significantly seen side effect in individuals using L-5-hydroxytryptophan as an oral supplement in recommended dosages of 100mg-200mg.

N-acetylserotonin is not metabolized to serotonin. Fillion et al. 1994 injected mice i.p. with N-acetylserotonin at higher levels e.g. 30mg/kg and no behavioral symptoms characteristic of the serotonin syndrome were observed (ref. 25). Injection of N-acetylserotonin proper leads to its rapid conversion to melatonin in rats (ref. 3.). The rate limiting step in melatonin synthesis is N-acetylation.

In premarket tests, conducted in the Netherlands, administration of N-acetylserotonin 75 mg orally in male and female subjects for 90 days resulted in no adverse responses. Intravenous administration of 3mg N-acetylserotonin in a human volunteer nightly for one month produced no adverse behavioral or mental changes. Over a year later no adverse effects are reported.

Dietary supplementation with melatonin 2 and 4mg in humans results in physiological levels of melatonin (ref. 20). Serum levels of N-acetylserotonin are higher than melatonin throughout the life cycle in men (Pang et al. 1985 ref. 16. abstract and data in English). Serum N-acetylserotonin levels are significantly higher in samples of women and men (Manz et al. 1985 ref. 17.) (Wolfer et al. ref. 6.).

In vitro studies using human lymphocytes indicate N-acetylserotonin to be a physiological antioxidant superior to its metabolite melatonin (Wolfer et al. 1999 ref. 6.). Endogenous antioxidants such as ascorbate (vitamin C), N-acetylserotonin, and tocopherols (vitamin E) can be prooxidants in high concentrations under some in vitro conditions. This oxidant potential is through the classic mechanism of hydrogen donation. In human red blood cells N-acetylserotonin reduced consumption of Vitamin E in models of oxidative stress (Barrachi et al. 1998 ref. 18).

Heartmind Nutrition has considered all available information in its determination of a reasonable expectation of safety for N-acetylserotonin as a new dietary ingredient. The scientific literature and premarket consumption continue to support the intrinsic safety of this endogenous antioxidant in small oral doses.

References:

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