DEPARTMENT OF HEALTH & HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Public Health Service

Memorandum

Date MAY 28 1998

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

98 MAY 28 A11 :48

Subject 75-day Premarket Notification for New Dietary Ingredient

To Dockets Management Branch, HFA-305

New Dietary Ingredient:	S-adenosylmethionine
Firm:	Nutramax Laboratories, Inc.
Date Received by FDA:	May 27, 1998
90-day Date:	August 24, 1998

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 August 24, 1998.

Robert J. Moore, Ph.D.

95S-0316

RPT 32

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington, DC 20204

MAY 28 1998

Todd R. Henderson, D.V.M.
Vice President
Nutramax Laboratories, Inc.
5024 Campbell Boulevard
Baltimore, Maryland 21236

Dear Dr. Henderson:

This is to notify you that your submission pursuant to 21 U.S.C. 350b(a) (section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)) dated May 26, 1998, concerning the marketing of a substance that you assert is a new dietary ingredient (i.e., S-adenosylmethionine) was received by the Food and Drug Administration (FDA) on May 27, 1998. Your submission will be kept confidential for 90 days from the date of receipt, and after August 24, 1998, 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.

The date that the agency received your notification submitted under 21 U.S.C. 350b(a), May 27, 1998, is the filing date for the notification. In accordance with the requirements of 21 U.S.C. 350b, for 75 days after the filing date, Nutramax Laboratories, Inc. shall not introduce, or deliver for introduction, into interstate commerce any dietary supplement that contains the new dietary ingredient S-adenosylmethionine.

Please contact us if you have questions concerning this matter.

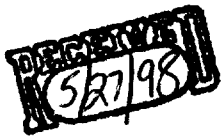
Sincerely,

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

The Nutraceutical Company
nutramax
LABORATORIES, INC.

59343

May 26, 1998



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

RE: Notification of New Dietary Ingredient

Dear Office of Special Nutritionals:

Pursuant to the Dietary Supplement Health and Education Act of 1994 (DSHEA), 21 USC § 350b(a)(2), and consistent with the final regulations published by the FDA in the Federal Register of September 23, 1997 (62 Fed. Reg. 49886-49892), 21 CFR § 190.6, "Requirements for Premarket Notification," Nutramax Laboratories, Inc. ("Nutramax Laboratories") hereby submits the following information concerning a new dietary ingredient that Nutramax Laboratories intends to begin marketing for use in dietary supplements. Pursuant to the applicable provisions of DSHEA, Nutramax Laboratories will not introduce the ingredient or deliver it for introduction into interstate commerce until at least 75 days after the date FDA receives this notification.

(1) NAME AND ADDRESS OF MANUFACTURER

The name and complete address of the manufacturer of the new dietary ingredient/supplement are as follows:

Distributor of the supplement:

Nutramax Laboratories, Inc.
5024 Campbell Boulevard
Baltimore, Maryland 21236
Phone: (410) 931-4000

Manufacturer of the active agent:

Knoll BioResearch S.A.
CH-6592 S. Antonino
Switzerland
Phone: 091 851 91 91

Manufacturer of the stabilized tablet (supplement):

Knoll Farmaceutici Spa
Via Europa 35
I-20053 Muggio MI
Italy
Phone: 039 24426

(2) NAME OF NEW DIETARY INGREDIENT

The name of the new dietary ingredient is:

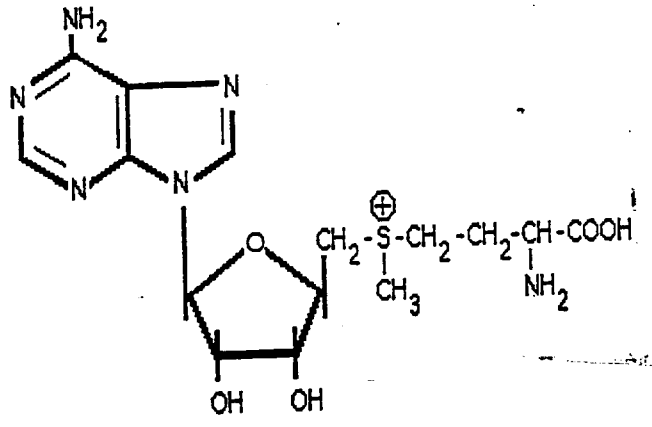
S-Adenosylmethionine (SEE STRUCTURAL FORMULA BELOW)

(3) DESCRIPTION

The description of the new dietary ingredient is as follows:

S-Adenosylmethionine is a white odorless amorphous powder with the structural formula shown below.

STRUCTURAL FORMULA



RANGE OF USE:

40 mg/day to 1600/mg/day

SAMe STRUCTURE AND FUNCTION CLAIMS:

S-Adenosylmethionine (SAMe) is a metabolite of the amino acid methionine that functions in a wide variety of biologic reactions in the body. It is found in all living cells and is an important intermediate in many pathways. SAMe is synthesized endogenously from methionine and adenosine triphosphate in a catalyzed reaction primarily in the liver. SAMe is needed for optimal hepatic function and has been shown to be depleted when the liver is stressed. When depleted, there is a reduction in hepatocellular membrane fluidity and a failure to secrete bile acids effectively. This membrane alteration is positively correlated with the amount of liver dysfunction.

SAMe is the initiator of three important metabolic pathways- transmethylation, transsulfuration and aminopropylation.

The transmethylation pathway involves the transfer of methyl groups from SAMe to a broad range of molecules such as phospholipids, nucleic acids, proteins and porphyrins. When SAMe induces methylation of liver plasma membrane phospholipids, the result is enhanced membrane fluidity which maintains membrane structure and function, which in turn improves the structure and function of the liver tissue. Alcohol induced liver dysfunction can deplete SAMe and result in interference with the transmethylation pathway and promote liver plasma membrane injury. SAMe is the precursor to all methylated compounds. These mechanisms are needed for optimal liver function and can be depleted when the liver is stressed.

SAMe is a methyl donor and by release of methyl groups initiates transsulfuration which generates sulfur compounds. This source of endogenous sulfur has many positive benefits in hepatic function by enhancing liver detoxification. SAMe increases the sulfation of hepatotoxic endogenous bile acids.

SAMe is also the precursor of essential amino acids and peptides including cysteine, taurine and glutathione. All of these are needed for optimal liver function and when depleted cause serious problems in liver function. Taurine

is implicated in the process of bile acid conjugation. Since bile acids conjugate with taurine, this increases their solubility and reduces the accumulation of toxic bile acids in the hepatocyte. An impairment of the transulfuration pathway can lead to a cysteine and taurine, deficiency which may cause nutritional defects particularly in people with liver dysfunction. Cysteine deficiency can lead to reduced production of the essential peptide glutathione. Glutathione acts as an intracellular detoxifying agent and is important in maintaining hepatic function. Glutathione protects the liver by neutralizing free radicals, which have a deleterious effect on all tissues in the body.

SAMe also has applications in optimizing joint structure and function, by stimulating proteoglycan synthesis. Proteoglycans are needed for optimal joint function. Evidence has shown that SAMe is a precursor of endogenous sulfated products, which are in turn used to sulfate glycosaminoglycans. SAMe has the ability to stimulate proteoglycan synthesis and secretion in cultured chondrocytes, which are important for cartilage repair. Oral dosing of SAMe induces a significant increase in synovial fluid concentration of this molecule. It is also involved in aminopropylation reactions to form polyamines as a stabilizing effect on proteoglycans. It also has protective effects on the gastric mucosa, and will not harm the mucosa as some NSAID's can. It also works as a scavenger of toxic oxygen species in the body, including the joint tissues, which can benefit joint structure and function.

S-Adenosylmethionine (SAMe) is present in many tissues, including the central nervous system (brain and spinal cord). In the CNS, as in the rest of the body, a major function of SAMe is to donate methyl groups in the reactions synthesizing various crucial compounds, including neurotransmitters (e.g., epinephrine) and phospholipids. For example, SAMe facilitates the conversion of phosphatidylethanolamine to phosphatidylcholine, which forms part of the inner lipid layer of the plasma membrane. In so doing, it increases membrane fluidity. This fluidity is necessary for the exchange of chemical messages (neurotransmitters) between brain cells. Thus, SAMe supports the synthesis of neurotransmitters, and also facilitates their function as chemical messengers in the brain.

(4) BASIS FOR THE SAFETY OF S-ADENOSYLMETHIONINE (SAMe)

S-Adenosylmethionine (SAMe) is a metabolite of the amino acid methionine that functions in a wide variety of biologic reactions in the body. It is found in all living cells and is an important intermediate in many pathways. SAMe is synthesized from methionine and adenosine triphosphate (ATP) by S-Adenosylmethionine synthetase (ATP-L-methionine-S-adenosyltransferase). SAMe is an important physiologic compound that occurs in every living cell and takes part in several biologic reactions either as a group donor or as an enzymatic inducer. It is needed for optimal hepatic function and has been shown to be depleted when the liver is stressed. When depleted, there is a reduction in hepatocellular membrane fluidity and a failure to secrete bile acids effectively. This membrane alteration is positively correlated with the amount of liver dysfunction.

The involvement of SAMe in three important biochemical pathways, i.e., transmethylation, transsulfuration, and aminopropylation, depends on its particular structure with a positive charge on the sulfur atom, which favors the cleavage of the sulfur-carbon bonds. The major metabolic pathways involving SAMe are outlined in the attached schematic in Exhibit 1.

The transmethylation pathway involves the transfer of methyl groups from SAMe to a broad range of molecules such as phospholipids, nucleic acids, proteins and porphyrins. In higher organisms, more than 40 either anabolic or catabolic reactions involve the transfer of the methyl group of SAMe to various substrates such as nucleic acids, proteins, and lipids, among others. When SAMe induces methylation of liver plasma membrane phospholipids, the result is enhanced membrane fluidity which maintains membrane structure and function, which in turn improves the structure and function of the liver tissue. Alcohol induced liver dysfunction can deplete SAMe and result in interference with the transmethylation pathway and promote liver plasma membrane injury. SAMe is the precursor to all methylated compounds. The methalated compounds are needed for optimal liver function and can be depleted when the liver is stressed.

SAMe is a methyl donor and by release of methyl groups initiates transsulfuration which generates sulfur compounds. SAMe, after giving its methyl group to different acceptors, is converted into S-adenosylhomocysteine, which is rapidly hydrolyzed to adenosine and homocysteine. The latter compound is then converted to cysteine, which can

exert a reducing effect either by itself or as an active part of glutathione, the main cell anti-oxidant. This source of endogenous sulfur has many positive benefits in hepatic function by enhancing liver detoxification. SAMe increases the sulfation of hepatotoxic endogenous bile acids.

SAMe is also the precursor of essential amino acids and peptides including cysteine, taurine and glutathione. All of these are needed for optimal liver function and when depleted cause serious problems in liver function. Taurine is implicated in the process of bile acid conjugation. Since bile acids conjugate with taurine, this increases their solubility and reduces the accumulation of toxic bile acids in the hepatocyte. An impairment of the transsulfuration pathway can lead to a cysteine and taurine, deficiency which may cause nutritional defects particularly in people with liver dysfunction. Cysteine deficiency can lead to reduced production of the essential peptide glutathione. Glutathione acts as an intracellular detoxifying agent and is important in maintaining hepatic function. Glutathione protects the liver by neutralizing free radicals, which have a deleterious effect on all tissues in the body.

Polyamine synthesis is another important metabolic pathway in which SAMe takes part. After being transformed into a decarboxylated analogue (DecaSAMe) by SAMe decarboxylase, the aminopropyl group is transferred to putrescine to form polyamines, whereas the remaining portion of the molecule gives rise to methylthioadenosine.

In addition to the biochemical pathways above, SAMe is also involved in proteoglycan synthesis which can optimize joint structure and function. Proteoglycans are needed for optimal joint function. Evidence has shown that SAMe is a precursor of endogenous sulfated products, which are in turn used to sulfate glycosaminoglycans. SAMe has the ability to stimulate proteoglycan synthesis and secretion in cultured chondrocytes, which are important for cartilage repair. Oral dosing of SAMe induces a significant increase in synovial fluid concentration of this molecule. It is also involved in aminopropylation reactions to form polyamines as a stabilizing effect on proteoglycans. It also has protective effects on the gastric mucosa, and will not harm the mucosa as some NSAID's can. It also works as a scavenger of toxic oxygen species in the body, including the joint tissues, which can benefit joint structure and function.

S-Adenosylmethionine (SAMe) is also present in many tissues, including the central nervous system (brain and spinal cord). In the CNS, as in the rest of the body, a major function of SAMe is to donate methyl groups in the reactions of synthesizing various crucial compounds, including neurotransmitters (e.g., epinephrine) and phospholipids. For example, SAMe facilitates the conversion of phosphatidylethanolamine to phosphatidycholine, which forms part of the inner lipid layer of plasma membrane. In so doing, it increases membrane fluidity. This fluidity is necessary for the exchange of chemical messages (neurotransmitters) and also facilitates their function as chemical messengers in the brain.

Information leading to the conclusion that SAMe will be safe when used in accordance with the ordinary conditions of use were culled from literature reviewing both animal and human studies. The conclusion of these studies is that SAMe is well tolerated in humans over extended periods of use.

The article Pharmacologic Aspects of S-Adenosylmethionine by G. Stramentinoli, Ph.D., reports that rats were tested for the effect of the ingredient on the gastrointestinal mucosa. The oral administration of single dose or repeated dose of up to 1,200 mg/kg for 30 days did not affect the integrity of the mucosal tissue, "suggesting that SAMe does not interfere with the cytoprotective function of prostaglandins in gastrointestinal tissue."

Italian Double-Blind Multicenter Study Comparing S-Adenosylmethionine, Naproxen, and Placebo in the Treatment of Degenerative Joint Disease, by I. Caruso, M.D. and V. Pietrogrande, M.D. studied, in part, the tolerability of S-Adenosylmethionine in comparison to naproxen and a placebo. SAMe was administered at a dose of 1200 mg/day to 734 patients for 30 days. The tolerability of SAMe was significantly better than naproxen both in terms of patient and physician judgments (79.3% of the physicians and 75.6 % of the patients judged the tolerance "good" to "excellent") and in terms of the patients side effects. There was no difference reported between the placebo and SAMe in the number of side effects.

A New Medical Approach to the Treatment of Osteoarthritis, Report of an Open Phase IV Study with Ademetionine[1] (Gumbaral), by R. Berger, M.D. and H. Nowak, Ph.D., reports result from a Phase IV study involving 20,641

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[1] Ademetionine is a synonym for S-Adensylmethionine.

patients being treated for eight weeks. No serious adverse drug effects were witnessed which "indicates a very high level of drug safety in the field of antirheumatics." The tolerability was judged by 87% of the physicians as "good" to "very good" with 8% and 5% judging it "moderate" and "poor" respectively.

A Long-Term (Two Year) Clinical Trial with S-Adenosylmethionine for the treatment of Osteoarthritis, by B. Konig, M.D., followed 108 patients with osteoarthritis of the knee, hip, and spine. The patients received 600 mg/day of SAMe for the first two weeks followed by 400 mg/day thereafter. The article concludes that the administration of SAMe was "well tolerated" which was confirmed by the low number of non-specific observed side effects.

Double-Blind Multicentre Study of the Activity of S-Adenosylmethionine in Hip and Knee Osteoarthritis, by S. Glorioso, S. Todesco, A. Mazzi, R. Marcolongo, M. Giordano, B. Colombo, G. Cherie-Ligniere, L. Mattara, G. Leardini, M. Passeri and M. Cucinotta D., conducted their study on 150 patients, who had been suffering of mono- or bi-lateral hip or knee joint osteoarthritis, at five clinical centers as a controlled, double blind and randomized study. The patients were allocated to either SAMe or ibuprofen treatment at a dose of 1200 mg/day for 30 days. The study concluded that there was an excellent tolerability in the SAMe treated group and that the treatment was not withdrawn throughout the study. Only minor gastrointestinal side effects were observed (five patients in SAMe group and 16 in ibuprofen group). The results of the laboratory test, did not differ significantly from normal.

Multicentre Double-Blind Placebo-Controlled Study of Intravenous and Oral S-Adenosyl-L-Methionine (SAMe) in Cholestatic Patients with Liver Disease by G. Manzillo, F. Piccinino, C. Surrenti, M. Frezza, G.A. Giudici and C. Le Grazie, followed 343 patients with intra hepatic cholestasis through 2 week intravenous SAMe at a dose of 800 mg/day or placebo, then the responding patients were subsequently allocated to receive either oral SAMe 1600 mg/day or placebo for 8 weeks. They concluded that intravenous or oral SAMe was as well tolerated as placebo without premature withdrawal from the study. No adverse effects occurred in either group.

Neuropharmacology of S-Adenosyl-L-Methionine, by Ross J. Baldessarini, M.D., mentioned in this review article the extensive use of enteric-coated oral preparations of SAMe in relatively high doses, above 1 gram per day, for the

treatment of thousands of patients with osteoarthritis, usually elderly, without evidence of significant toxicity. The most typical side effects were mild upper gastrointestinal symptoms, but the incidence of even those had sometimes been lower than the rate of side effects with commonly used anti-inflammatory agents such as ibuprofen or even non-specific side effects of placebo treatment.

Finally, S-Adenosylmethionine in the treatment of Osteoarthritis, Review of the Clinical Studies, by C. Di Padova, M.D., summarizes the various experimental and clinical studies noted above as well as others. The conclusion of the article is that when looking at the results of the various studies, the results " indicate that SAMe is well tolerated by the gastric mucosa and other organs." Further the article concludes that this lack of effect "confirms the recent data of Stramentinoli who did not find any interference of SAMe with the eicosanoid system."

Another study reviewed in the article, conducted by Tritapepe, confirmed the tolerance of SAMe through treatment of seven healthy volunteers. Each volunteer was treated with 1.2 g per day of SAMe for a period of four weeks. Endoscopic and histologic evaluation was preformed on the stomach and duodenum both before and after treatment with no evidence of toxicity being documented.

Copies of the articles used to reach the conclusion that the new dietary ingredient is safe are attached.

Respectfully Submitted

NUTRAMAX LABORATORIES, INC.

By:_____
Todd R. Henderson, D.V.M.
Vice-President

Attachments

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Exhibit A

Major metabolic pathways involving SAMe (Stramentinoli, 1987) [12]