



DEPARTMENT OF HEALTH & HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

Public Health Service

Memorandum

Date . DEC -3 1999

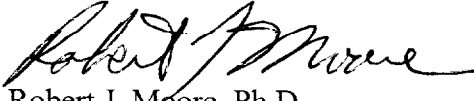
From Senior Regulatory Scientist, Regulatory Branch, Division of Programs & Enforcement Policy (DPEP), Office of Special Nutritionals, HFS-456

Subject 75-day Premarket Notification for New Dietary Ingredient

To Dockets Management Branch, HFA-305

New Dietary Ingredient:	Leci-GHA (choline alfoscerate-enriched phospholipid)
Firm:	Lucas Meyer, Inc.
Date Received by FDA:	September 20, 1999
90-day Date:	December 18, 1999

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 February 17, 2000.

  
Robert J. Moore, Ph.D.



DEC - 3 1999

Food and Drug Administration  
Washington, DC 20204*Rec'd 12/8/99  
JB*

Mr. Daniel A. Kracov, Esq.  
Patton Boggs LLP  
2550 M Street, N.W.  
Washington, DC 20037-1350

Dear Mr. Kracov:

This letter is in response to your letter to the Food and Drug Administration (FDA) dated September 17, 1999, on behalf of Lucas Meyer, Inc. (PO Box 3218, Decatur, Illinois), making a submission for a new dietary ingredient pursuant to 21 U.S.C. 350b(a)(2) (section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act). Your letter notified FDA of your intent to market a product containing a new dietary ingredient named Leci-GHA, a choline alfoscerate-enriched phospholipid.

21 U.S.C. 350b(a)(2) requires that a manufacturer or distributor of a dietary supplement that contains a new dietary ingredient submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate 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 section 350b(a)(2), there must be a history of use or other evidence of safety establishing that the dietary 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.

FDA has carefully considered the information in your submission, and the agency has concerns about the evidence on which you rely to support your conclusion that a dietary supplement containing Leci-GHA will reasonably be expected to be safe. Your submission contained the results of several human and animal studies and other information that you assert are adequate to evaluate the safety of ingested Leci-GHA.

The submission stated that Leci-GHA is a choline-alfoscerate-enriched phospholipid and that choline alfoscerate is a phospholipid precursor in choline biosynthesis. The submission, however, contained no specific data from studies of exposure to oral Leci-GHA, the enriched phospholipid compound that is the new dietary ingredient. The evidence that the firm relied upon as a basis for their conclusion that the dietary supplement containing Leci-GHA will reasonably be expected to be safe comes from studies conducted using only choline alfoscerate. There is no information that explains a basis for concluding that there is a sound scientific basis to extrapolate these findings to exposure to Leci-GHA, which contains other substances in addition to choline alfoscerate. Moreover, the submission did not describe the percent enrichment of the phospholipid with choline alfoscerate, which precludes comparing, with certainty, the recommended dosage of Leci-GHA with the dosages of choline alfoscerate using in the studies contained in the submission.

*955-0316**RPT60*

The firm stated in its submission that choline alfoscerate is a typical component of many common foods, such as vegetable lecithins and lecithins present in eggs and cow's milk. However, the submission contained no quantitative estimates of the actual human diet exposure to choline alfoscerate. Additionally, the submission did not address differences, if any, in the absorption or bioavailability of choline alfoscerate in foods or the new dietary ingredient. Therefore, no comparisons between typical dietary exposure to choline alfoscerate and the exposure to this substance that would result from the use of the proposed dietary supplement can be reliably made.

The submission contained several articles that reported the results of one or more studies that described the use of choline alfoscerate in humans and animals. Several of the articles describe the results of studies of choline alfoscerate in patients with brain injuries from cerebral ischemic events, multi-infarct dementia, vascular dementia, or senile organic brain syndrome. Except for one study, these studies were of choline alfoscerate administered by non-oral routes. These studies reported several side effects, such as headache, confusion/dizziness, erythema, and excitation/insomnia. While the authors of these studies generally considered these side effects to be mild effects that occurred at a relatively low incidence, for several reasons, we question whether these studies can support a conclusion that, when used in a dietary supplement as proposed, Leci-GHA can be reasonably expected to be safe. First, only one article reported findings from a study using orally-administered choline alfoscerate. Second, most of the studies were conducted to study the pharmacological effects or efficacy of intravenously administered or injected choline alfoscerate in sick patients. Moreover, none of the studies submitted were designed nor intended to examine the adverse or toxicological effects of choline alfoscerate in healthy people; instead, the dietary ingredient was used as a therapy in studies of persons with serious diseases. Such studies have limited utility for determining whether the long-term use of a substance as an ingredient in dietary supplements is safe because they do not provide dose-response data nor measurements of endpoints of toxicological concern. Third, the findings from the studies reported several side effects that reflect changes in cognitive and behavioral function. The studies also reported other changes in cognitive and behavioral function and personality and psychometric test measures that were considered to be beneficial. Taken together, all of these findings seem to point to choline alfoscerate contributing to changes in central nervous system neurochemical function. Although some of these changes may be of potential clinical significance in persons with the conditions described in the studies, the significance of these central nervous system effects in otherwise healthy persons of different age groups, especially children, can not be determined from these studies. In fact, the studies are designed in a manner that limits the use of the findings obtained from them as an adequate basis to conclude that the reported central nervous system actions of choline alfoscerate are not of concern to healthy persons using dietary supplements containing it for an extended period of time.

The submission also contained the results of two studies in healthy young subjects given oral choline alfoscerate. The investigators who conducted these studies stated that no significant adverse side effects were noted, although they reported that there were some choline alfoscerate-induced changes in certain sleep measurements, such as total time awake, number of awakenings, sleep efficiency, and rapid eye movement density. These two studies were of short duration (10 days and 7 days) and were not designed to investigate potential adverse effects. The findings from experimental exposures of such short duration do not provide an adequate basis to conclude that no untoward effects would be expected from the oral consumption of the test substance for longer periods of time, such as would be expected if it was used as a dietary supplement.

The submission also contained summary data from animal studies that the firm stated support a conclusion that Leci-GHA is safe. No accompanying data or other information, other than the descriptive summaries, for these studies were included in the submission. A review of the findings from the animal data shows that: (1) the lethal dose of choline alfoscerate is \_\_\_\_\_ in mice and rats and \_\_\_\_\_ in dogs; (2) chronic (26 weeks) oral exposure of rats to choline alfoscerate resulted in a no observable adverse effect level (NOAEL) of \_\_\_\_\_ and a lowest observable adverse effect level (LOAEL) of \_\_\_\_\_<sup>1</sup>; (3) chronic (26 weeks) oral exposure of dogs to choline alfoscerate resulted in a NOAEL of \_\_\_\_\_ and a LOAEL of \_\_\_\_\_<sup>2</sup>.

It is difficult to determine the exact nature of the toxicological and/or clinical significance of the choline alfoscerate-induced physiological and behavioral changes because the primary data was not provided. However, for the purposes of examining the potential hazardous nature, if any, of these effects, we used a typical safety assessment approach to estimate an allowable daily intake (ADI) for choline alfoscerate based on the most sensitive toxicological endpoint in the animal studies (in this case, the most sensitive toxicological endpoints are the adverse effects observed in dogs at the LOAEL dose of \_\_\_\_\_. Therefore, the safety assessment would be based on the corresponding NOAEL (i.e., \_\_\_\_\_) using an uncertainty factor of 100 (a uncertainty factor of 10 for intra- and a uncertainty factor of 10 for inter-species variability). The safety assessment results in an ADI for choline alfoscerate of \_\_\_\_\_.

To compare the ADI obtained from the data for the animal studies, it is necessary to assume that exposure to choline alfoscerate is comparable to exposure to Leci-GHA and that a dose of choline alfoscerate would represent an equivalent dose of Leci-GHA. The recommended dose of Leci-GHA for the dietary supplement containing it is 1 g/d (17 mg Leci-GHA/kg BW/d for a 60 kg adult). Using these assumptions, the recommended dose results in a daily exposure that is \_\_\_\_\_ the ADI for choline alfoscerate. This suggests that the chronic use of the dietary supplement containing Leci-GHA that is the subject of the new dietary ingredient notification may be associated with adverse effects. More information is needed about the nature and degree of the adverse effects seen in animals in order to have more certainty in the safety assessment.

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that Leci-GHA, when used under the conditions recommended or suggested in the labeling of your product, 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 under 21 U.S.C. 331(a) and (v).

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<sup>1</sup>The critical effects associated with the LOAEL in rats were reduced mobility and reactivity (i.e., behavioral depression).

<sup>2</sup>The critical effects associated with the LOAEL in dogs were lethargy, decreased food intake and body weight, and some changes in blood chemistry values.

Page 4 - Mr. Daniel A. Kracov, Esq.

Please contact us if you have questions concerning this matter.

Sincerely,

A handwritten signature in black ink, appearing to read 'Lynn A. Larsen', with a long horizontal flourish extending to the right.

Lynn A. Larsen, Ph.D.

Director

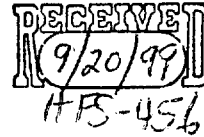
Division of Programs and Enforcement Policy

Office of Special Nutritionals

Center for Food Safety

and Applied Nutrition

September 17, 1999



Daniel A. Kracov  
(202) 457-5623  
dkracov@pattonboggs.com

VIA COURIER

Dr. Robert J. Moore  
Office of Special Nutritionals (HFS-450)  
Center for Food Safety and Applied Nutrition  
Food and Drug Administration  
200 C St. SW  
Washington, DC 20204

Re: New Dietary Ingredient Notification: Leci-GHA™

Dear Dr. Moore:

Enclosed please find an original and two copies of the "Notification of the Marketing of a New Dietary Ingredient: Leci-GHA," submitted pursuant to section 413 of the Federal Food, Drug, and Cosmetic Act, on behalf of Lucas Meyer Inc. Please note that pursuant to 21 C.F.R. § 20.61, Lucas Meyer designates as confidential Section C.2. of the notification (Safety Studies, Animal), and the Investigator's Brochure at Attachment 11.

Thank you for your attention to this matter. If you have any questions relating to the notification, please do not hesitate to call me at the above number.

Sincerely,

A handwritten signature in black ink, appearing to read "DAK", with a long horizontal flourish extending to the right.

Daniel A. Kracov

DAK/jjs

Enclosure

# Notification of the Marketing of a New Dietary Ingredient

## Leci-GHA™

Pursuant to section 413 of the Federal Food, Drug, and Cosmetic Act, Lucas Meyer Inc., located at P.O. Box 3218, Decatur, Illinois, 62524-3218, hereby notifies the Food and Drug Administration that it will market the new dietary ingredient, Leci-GHA. Leci-GHA is a choline alfoscerate-enriched phospholipid compound. Choline alfoscerate is a phospholipid precursor in choline biosynthesis, and is known by a variety of different chemical names, including choline alfoscerate, glycerolphosphorylcholine ("GPC"), glycerylphosphorylcholine, glycerylphosphorcholine, and glycerophosphorocholine.

### I. Dietary Supplements Containing Choline Alfoscerate

Lucas Meyer will market Leci-GHA for use in dietary supplements at a maximum level of 1 gram/day. The labeling of Leci-GHA will state that it is for use to support and maintain the intrinsic production and release of growth hormone within the body.

### II. Evidence of Safety

#### A. Introduction

Leci-GHA, when used under the conditions recommended in the indicated labeling, is reasonably expected to be safe. Choline alfoscerate is naturally supplied to the body as acylated compounds, such as vegetable lecithins, or animal lecithins from eggs or cow milk,<sup>1</sup> and serves as a source of choline that is easily absorbed by the intestine.<sup>2</sup> Choline alfoscerate is a direct precursor of acetylcholine, a chemical important in muscle contraction and transmission of neuroimpulses. Choline alfoscerate products are currently marketed in foreign countries.<sup>3</sup> In addition, a choline alfoscerate precursor, phosphatidylcholine, is an ingredient in nutritional supplements marketed in the United States.

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<sup>1</sup> M. Wahlgren, T. Drakenberg, H.J. Vogel and P. Dejmek, "<sup>31</sup>P-nuclear magnetic resonance study of milk reactions," *Journal of Dairy Research* (1986) 53, 539-545 (Attachment 1). There are approximately 250 mg of choline alfoscerate per liter of milk. Id.

<sup>2</sup> Diets deficient in choline have been shown to cause severe adverse effects in some species. Zeisel, S.H., "Dietary choline: biochemistry, physiology, and pharmacology." *Annu. Rev. Nutr.* 1981, 1, 95-121, at 96 (Attachment 2).

<sup>3</sup> These countries appear to include South Korea, Russia, Italy, Poland, Argentina, and Romania.

## B. Development and Manufacturing

Leci-GHA is developed using a patented method for preparing glycerophospholipids.<sup>4</sup> The method calls for performing alcoholysis and basic ion exchange on a deoleated soy lecithin.

## C. Safety Studies

### 1. Human

Choline alfoscerate has been marketed in several countries, numerous studies on its safety and effectiveness in humans for various drug uses have been conducted and published.<sup>5</sup> Although the intended use of choline alfoscerate as a dietary supplement differs from drug uses, the drug studies indicate the safety of choline alfoscerate in humans. The following section provides examples of human studies in which choline alfoscerate was shown to be safe for human use.

One study examined the clinical efficacy and tolerability of choline alfoscerate in a clinical open multi-center trial of 2044 patients suffering from recent stroke or transient ischemic attacks.<sup>6</sup> In phase one, 1gram/day choline alfoscerate was administered intramuscularly for 28 days, and in phase two, 1200 mg/day were administered orally for approximately 5 months. At the end of the six months, no deaths were attributed to the treatment, only 17 adverse events were reported during the oral phase, and only 4 subjects withdrew during the oral phase due to unwanted effects. Of the 4 withdrawals, 1 was with heartburn, 1 with diarrhea, 1 with skin rash, and 1 with dizziness or confusion. The most frequently reported side effects from both phases were heartburn, insomnia, nausea, and headache. This study clearly demonstrates a high human tolerability for choline alfoscerate.

Several studies have examined the effects of choline alfoscerate on multi-infarct dementia, and concluded that choline alfoscerate shows excellent tolerability.<sup>7</sup> In these studies, subjects with multi-infarct dementia were given 1 gram/day choline alfoscerate, intramuscularly, for 90 days. The studies used methods of determining tolerability such as assessing tolerability at injection site,<sup>8</sup> obtaining reports of local or systemic adverse

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<sup>4</sup> U.S. Patent No. 5,315,023, March 8, 1993. The patent summary appears at Attachment 3.

<sup>5</sup> To our knowledge, none of the studies of choline alfoscerate took place pursuant to an Investigational New Drug application filed with the Food and Drug Administration.

<sup>6</sup> Giuseppe Barbagallo Sangiorgi, et. al., "α - Glycerophosphocholine in the Mental Recovery of Cerebral Ischemic Attacks," *Annals of the New York Academy of Sciences*, Vol. 717, ed. Imre Zs.-Nagy, Denham Harman, and Kenichi Kitani, The New York Academy of Sciences: New York, New York, 1994, 253-265 (Attachment 4).

<sup>7</sup> A. Muratorio, et. al., "A neurotropic approach to the treatment of multi-infarct dementia using L-alpha glycerylphosphorylcholine. *Current Therapeutic Research*, vol. 52, no. 5, (1992): 741-752 (Attachment 5); R. DiPerri, "A multicentre trial to evaluate the efficacy and tolerability of alpha-glycerolphosphoryl-choline versus cytosine diphosphocholine in patients with vascular dementia," *J. Int. Med. Res.* (1991), Jul; 19(4):330-341 (Attachment 6); L. Frattola, et. al., "Multicenter Clinical Comparison of the Effects of Choline Alfoscerate and Cytidine Diphosphocholine in the Treatment of Multi-Infarct Dementia," *Current Therapeutic Research*, Vol. 49, no. 4, April 1991, 683-693 (Attachment 7).

<sup>8</sup> Muratorio, et. al., at 744; Di Perri, et. al., at 333.



reactions,<sup>9</sup> and testing vital signs and laboratory parameters.<sup>10</sup> The choline alfoscerate was well-tolerated in all three studies; side effects were limited and laboratory tests showed no clinically or statistically significant changes.<sup>11</sup> For example, in one study, only one subject dropped out due to side effects (headache and flushing), and headache, flushing, and erythema were the only side effects deemed treatment-related.<sup>12</sup>

Another study was conducted on forty male patients with senile organic brain syndrome of medium severity.<sup>13</sup> Subjects were given 1 gram/day choline alfoscerate, intramuscularly, for twelve weeks. No subjects withdrew from the study due to side effects, and the only reported side effect was of headache in one person.<sup>14</sup> Another study on 32 healthy volunteers who were given 1200 mg/day choline alfoscerate for ten days, did not show any significant side effects.<sup>15</sup>

A third study of interest showed that choline alfoscerate does not affect sleep. In this study, subjects were treated with 400 mg tablets of choline alfoscerate three times per day for 18 days. The subjects showed no alteration in sleep induction or maintenance or sleep stage percentages.<sup>16</sup>

## 2. Animal

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<sup>9</sup> Frattola, et. al., at 690.

<sup>10</sup> Muratorio, et. al., at 744, Frattola, et. al., at 690.

<sup>11</sup> Frattola, et. al., at 690.

<sup>12</sup> Di Perri, et. al., at 334, 336.

<sup>13</sup> D. Abbati, et. al., "Nootropic therapy of cerebral aging." *Advances in Therapy*, vol. 8, no. 6, (1991): 268-276.

<sup>14</sup> *Id.* at 272 (Attachment 8).

<sup>15</sup> N. Canal, et. al., "Effect of L-alpha-glyceryl-phosphorylcholine on amnesia caused by scopolamine." *Intl J Clinical Pharmacology, Therapy and Toxicology*, vol. 29, no. 3, (1991): 103-107 (Attachment 9).

<sup>16</sup> L. Ferini Strambi, "Choline Alfoscerate: Short-Term Effect on Sleep in Healthy Subjects," *Current Therapeutic Research*, Vol. 49, No. 4, April, 1991 (Attachment 10).

<sup>17</sup> Italfarmaco, "L- $\alpha$ -Glycerylphosphorylcholine ( $\alpha$ -GPC) Investigator's Brochure," Edition V, March 1997 (Attachment 11).



### *3. Conclusion*

Study results indicate that choline alfoscerate, a naturally occurring precursor, has been studied extensively in humans. Choline alfoscerate also has been studied in animals, and has not shown significant safety risks in doses exceeding that expected for humans. Thus, choline alfoscerate is reasonably expected to be safe as proposed for use in dietary supplements.

### III. Declaration of Confidentiality

Pursuant to 21 C.F.R. § 20.61, Lucas Meyer designates the following information as exempt from public disclosure:

- All information contained under Section C.2. of this notification (Safety Studies, Animal).
- The Investigator's Brochure at Attachment 11.

Respectfully Submitted,



Daniel A. Kracov, Esq.  
Patton Boggs LLP

on Behalf of  
Lucas Meyer Inc.

September 17, 1999

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Steven H. Zeisel, “Dietary Choline: Biochemistry, Physiology, and Pharmacology,” <i>Ann. Rev. Nutr.</i> , 1981, 1:95-121.	2
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Giuseppe Barbagallo Sangiorgi, Mario Barbagallo, Marcello Giordano, Maria Meli, and Rita Panzarasa, “ $\alpha$ -Glycerophosphocholine in the Mental Recovery of Cerebral Ischemic Attacks: An Italian Multicenter Clinical Trial, in “Pharmacology of Aging Processes: Methods of Assessment and Potential Interventions,” <i>Ann. New York Acad. Sci.</i> , Vol. 717, New York, New York, 1994, 253-269.	4
Alberto Muratorio, Ubaldo Bonuccelli, angelo Nuti, et al., “A Neurotropic Approach to the Treatment of Multi-Infarct Dementia Using L- $\alpha$ -Glycerolphosphorylcholine,” <i>Curr. Ther. Res.</i> , Vol. 52, No. 5, November 1992, 741-752.	5
R. Di Perri, G. Coppola, L.A. Ambrosio, A. Grasso, F.M. Puca and M. Rizzo , “A Multicentre Trial to Evaluate the Efficacy and Tolerability of $\alpha$ -Glycerolphosphorylcholine versus Cytosine Diphosphocholine in Patients with Vascular Dementia,” <i>J. Int. Med. Res.</i> 1991, 19: 330-341.	6
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Carlo Abbati, M.D., Giorgio Rondi, M.D., Rosangela Rosola, Francesca Vavassori, M.D., Angelo Bosio, M.D., “Nootropic Therapy of Cerebral Aging,” <i>Adv. Ther.</i> , Vol. 8, No. 6, November/December 1991, 268-276.	8
N. Canal, M. Franceschi, M. Alberoni, C. Castiglioni, P. De Moliner and A. Longoni, “Effect of L- $\alpha$ -Glyceryl-Phosphorylcholine on Amnesia Caused by Scopolamine,” <i>Int. J. Clin. Pharm. Ther. Tox.</i> , Vol. 29 No. 3 – 1991, 103-107.	9
L. Ferni Strambi, M. Zucconi, V. Castronovo, C. Erminio, A. Marcone, and S. Smirne, “Choline Alfoscerate: Short-Term Effect on Sleep in Healthy Subjects,” <i>Curr. Ther. Res.</i> , Vol. 49, No. 4, April 1991, 610-615.	10
“L- $\alpha$ -Glycerolphosphorylcholine ( $\alpha$ -GPC),” <i>Confidential Investigator’s Brochure</i> , Italfarmaco, V. Edition – March 1997.	11