DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: 12/03/02

From: Gloria Chang, IDS/Pharmacist, Division of Standards and Labeling Regulations, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-820

Subject: 75-Day Premarket Notification of New Dietary Ingredients

To: Dockets Management Branch, HFA-305

New Dietary Ingredient: BioDiamend (Lagerstroemia specious, L)

Firm: Kelatron Corp.

Date Received by FDA: 2/11/02

90-Day Date: 5/12/02

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached correspondence for the aforementioned dietary ingredient should be placed on public display in docket number 95S-0316 as soon possible. Thank you for your assistance.

Gloria Chang

Gloria Chang, IDS/Pharmacist

Attachments

95S-0316

RPT115

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
College Park, MD

APR 26 2002

Mary Ann Coral-Amasifuen
Kelatron Corporation World Headquarters
1675 West 2750 South
Ogden, Utah 84401

Dear Ms. Coral-Amasifuen:

This is in response to four separate notifications you submitted pursuant to 21 U.S.C. 350b(a)(2). All four notifications were received by the Food and Drug Administration (FDA) on January 3, 2002, followed by an addendum dated January 10, 2002. In follow up, we contacted you by telephone on January 14, 2002 notifying you that the notifications were incomplete (see background of follow up below). Subsequently, you sent addendums dated January 18, and February 5, 2002. We received your last addendum for your notifications dated February 5, 2002 on February 11, 2002. Therefore, the effective filing date for all four notifications is February 11, 2002.

As noted above, we contacted you by telephone on January 14, 2002 notifying you that the notifications were incomplete in that they did not contain levels of the dietary ingredients, conditions of use, or copies of the full-text journal articles corresponding to the abstracts you sent us. We explained that the requested information would have to be submitted in triplicate (3 copies) if we were to consider these references in our review. On January 24, 2002, we called you again and left a message that the addendums that you sent dated January 18, 2002, did not contain the levels of the new dietary ingredients as requested.

Each notification concerned a different botanical that you assert is a new dietary ingredient. The botanicals are listed below by the Latin binomial name, plant form, and product name as stated in your notifications.

Vitex negundo L. (pure leaf powder) -- BioVitaflu/BioVitabronch
Blumea balsamifera L. (pure leaf power) -- BioRenal
Mormadica charantia L.- Makiling v. (pure leaf powder) -- BioDiamed
Lagerstroemia specious L. (pure leaf powder) -- BioDiamend

The law at 21 U.S.C. 350b(a)(2) requires that a manufacturer or distributor submit certain information to FDA at least 75 days before a new dietary ingredient or a dietary supplement containing it is introduced or delivered for introduction into interstate commerce. This information must include the basis on which the manufacturer or distributor has concluded that the new dietary ingredient or a dietary supplement containing it 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 dietary ingredient, when used under the conditions recommended or suggested in the product's labeling, will reasonably be expected

to be safe. If this requirement is not met, the new dietary ingredient or dietary supplement containing it 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 considered the information in your notification and has several significant concerns. Based on the information in your notification for all four botanical ingredients, FDA has determined that the information submitted suggests that the intended uses imply or represent treatment of disease. The following are examples.

- The botanical ingredient *Vitex negundo* L., the product name "BioVitaflu/BioVitabronch" implies a recognizable disease condition, the "flu". FDA considers a brand name that includes a disease name or a clearly recognizable derivation of a disease name to be a disease claim. (See 21 CFR 101.93(g)(2)(iv)(A).)
- Under the conditions of use for the botanical ingredient *Blumea balsamifera* L. (BioRenal) you state that BioRenal might be effective as a diuretic and as an anti-urolithiasis agent (chronic formation of kidney stones).
- Under the conditions of use for the botanical ingredient *Mormadica charantia* L.-Makiling v. (BioDiamed) you state that the recommended use is that it may be helpful for blood sugar regulation and type II diabetes mellitus.
- Under the conditions of use for the botanical ingredient *Lagerstroemia specious* L.-(BioDiamend) you state that clinical trials indicated that BioDiamend may have some blood sugar lowering properties in vivo and therefore the recommended use is that it may be helpful for blood sugar regulation and type II diabetes mellitus.

Please be advised that any representation that a product is intended for the diagnosis, cure, mitigation, treatment or prevention of disease in man or animals suggests that it is a drug, as defined in 21 U.S.C. § 321(g)(1)(B), and would be subject to regulation under the drug provisions of the Federal Food, Drug and Cosmetic Act. All drugs must be approved by FDA before they can be marketed in the United States. If you wish to market your products as drugs, you should contact FDA's Center for Drug Evaluation and Research (CDER), Office of Compliance, HFD-310, 7520 Standish Place, Rockville, Maryland 20855.

FDA also has concerns about the evidence on which you rely to support your conclusion that the four botanical ingredients in your notifications will be reasonably expected to be safe for the suggested or intended uses.

Much of the history of use information you submitted appears to be selected pages printed from commercial magazines or promotional literature. Some of the sources of these articles were not identified nor were the specific ingredients in your notifications mentioned in the articles. These articles primarily focus on anecdotal use for disease conditions and do not address safety. The statements in these articles cannot be validated and are not corroborated

by scientific data. Although requested, you did not provide us with photostatic copies or reprints of all of the abstracts or the complete reference citation for what appears to be an excerpt from a reference book. Consequently, those abstracts and excerpts were not considered in our review.

We are also unsure if the botanical ingredients described in some of the scientific literature were the same as those described in your notifications. Further, we are not sure if the specific genus, species, and author citations are correct for two of the botanical ingredients. Although we searched a number of botanical databases, we could not find the specific Latin binomial names *Mormadica charantia* L. and *Lagerstroemia specious* L as stated in your notifications. We are aware of the Latin binomial names *Momordica charantia* L. or *Momordica charantia* Linn. and *Lagerstroemia speciosa* L. or *Lagerstroemia speciosa* (L.) Pers. However, when referring to your botanical ingredients in this letter, we will be using the Latin binomial names as stated in your notifications.

We also have concerns regarding the scientific information that was submitted. Most of the scientific articles and unpublished reports in your notifications primarily address use of the study ingredients as drugs to treat specific disease conditions and do not provide adequate evidence of the safe use of the specific ingredient. Also, it was not clear if the ingredients used in some of the studies were the same ingredients (genus, species, and author citation), the same part of the plant, or the levels per serving dose, as those stated in your notifications.

In your notification on *Vitex negundo* L (BioFlu/Bio Vitabronch), you submitted a summary of an unpublished, uncontrolled, open label study evaluating the safety and efficacy of *Vitex negundo* L (Lagundi) tablets as an antitussive agent. The trial titled Section 5.2:Phase II Clinical Trial was conducted from January to December 1984. Twenty-five subjects were enrolled, 20 children and 5 adults. Subjects were described as having acute asthma (n=4) or upper-respiratory, non-bacterial infection (n=21). There was a single concluding statement of safety that noted that there were no untoward side effects noted or volunteered. No details or specific data on safety was provided. We also note that the actual dose level in each tablet was not stated. Further, subjects with present or past disease conditions were explicitly not enrolled in the trial as stated in the exclusion criteria of the study. This is of particular concern since under your conditions of use there are no recommendations to restrict its use in persons with pre-existing disease conditions.

In the report of a randomized study comparing lagundi (15 mg/kg taken every 8 hours for 3 days) to theophylline (3 mg/kg taken every 8 hours for 3 days) for the treatment of acute asthmatic exacerbation (a disease condition), forty-three subjects were enrolled, however; 3 subjects dropped out after 24 hours. Twenty of the subjects were exposed to lagundi. The analysis was done on forty subjects, 6 males and 34 females. For almost all outcome measures the theophylline group was superior to the lagundi group. Adverse events were noted for 8 theophylline subjects and 5 in the lagundi group. In the lagundi group, the side effects noted were emesis (2 cases), palmar desquamation (2 cases) and increased urinary frequency (1 case). The author did not comment on the subjects that developed palmar

desquamation. The author also expressed concerns about the inadequacy of this study and recommended further evaluation and investigation of lagundi.

We also have concerns regarding the short exposure time to lagundi. The total clinical exposure cited as a safety database consists of only approximately 45 individuals with only a maximum exposure to lagundi of 72 hours. Considering that you did not indicate any limitation or duration of use, these studies do not address chronic use or long term use. Further, we have concerns that subpopulations with present or past medical conditions that were excluded in the study, were not recommended for exclusion under your conditions of use. Accordingly, the study cannot support the conclusion that lagundi is reasonably expected to be safe if marketed as a new dietary ingredient for the intended or suggested use.

In the notification for *Blumea balsamifer* L. (BioRenal), you submitted sections of a larger unpublished study labeled as "7.0 CLINICAL TRIALS." The subsections are; 7.1 "Phase I: Sambong Tablet as Diuretic", 7.2 "Phase II:Clinical Trial of Sambong Tablet as Diuretic," 7.3 "Phase II:Sambong Tablet as anti-urolithiasis," 7.4, "Phase III clinical Trial of *Blumea balsamifer* L (Sambong) tablet in the treatment of urinary tract stone: a randomized double-blind placebo-controlled study", and 7.5 "Extended Phase III Open Trial of *Blumea balsamifer* L (Sambong) for the treatment of urinary tract stones."

All of the studies were small. Overall, 59 subjects were exposed to Sambong across all 5 studies. Exposure time ranged from 2 days to a maximum of approximately 6 weeks. Most of the exposures were less than 6 weeks.

In the studies for diuretic use, we have the following specific comments. No mechanism for the diuretic activity was ascertained, yet based on the conclusions reached that the diuretic effect of Sambong was comparable to thiazide diuretics, Sambong use may pose a safety risk in a normal population or in a subpopulation who may be also using other diuretics. The studies did not sufficiently address safety. Based on the conclusions in the study that Sambong tablets produced statistically significant diuresis and chloriuresis comparable to hydrochlorthiazide given at 50 mg in 2 divided doses, we have concerns that this may pose an electrolyte imbalance risk in normal populations or in a subpopulation with certain present or past medical conditions. Your recommended conditions of use only excluded use in lactating or pregnant women. Your recommended use in adults 18 years old and over neither included instructions on limitations or duration of use nor excluded use for any other populations that may be at risk either for using diuretics or due to concurrent use of other diuretic agents.

In addition, we have concerns regarding the implied use of BioRenal to treat or prevent kidney stones, a disease condition. We have significant safety concerns that consumers will not be able to self diagnose this specific disease condition and that prolonging medical treatment may lead to more serious health consequences.

In your notification for *Mormadica charantia* L.- Makiling v. (BioDiamed), the only full text journal article, was a general summary on the anti-diabetic properties and phytochemistry of a

botanical *Momordica charantia* L. Please note the difference in the Latin binomial names for your botanical ingredient and the botanical cited in the article. The article primarily focuses on general efficacy, and not the safety of the seeds or juice of the plant. It does not address the specific plant part or form (the pure leaf powder) or the serving levels as that of your ingredient. Further, the *in vivo* animal studies information presented a general overview of referenced toxicity studies and focused primarily on the juice or extracts of Karela. You did not provide the referenced full text journal articles in your notification. We are unsure if Karela is the same plant source or plant form as your ingredient. Nonetheless, the animal toxicity information did not provide any dosing levels used nor did it address the specific plant form described in your notification.

Thus, we conclude that the evidence of safety from the article was minimal or lacking and no conclusions of safety can be drawn from the report. We also cannot draw any safety conclusions from the other published report on the hyperglycemic activity of polypeptides of a plant source (fruit, seeds, and tissue). That report focuses on a peptide isolated from the seeds and tissue of a botanical variety, *Momordica charantia* Linn. and does not describe the specific plant part (pure dried leaf powder) described in your notification. Further, the report primarily addresses hypoglycemic activity of the peptide and the only safety information is a statement that referenced a study using a polypeptide-p-ZnCl in three juvenile patients. A photostatic copy or reprint of the full published text of that citation reference was not included in your submission. Thus, no conclusions regarding safety can be drawn from the report.

In your notification for *Lagerstroemia specious* L., the study submitted appears to be an unpublished trial titled "The Clinical Study on the Water Extract of Leaves of *Lagerstroemia specious* L for Mild Cases of Diabetes Mellitus." Twenty-four subjects over the age of 20 years were studied. There is very little information on safety in this report and it is unclear if the study was a single or double-blinded study, a critical concern in safety analysis. The only statement regarding safety was a statement that all 24 subjects did not have any adverse effects. In the absence of detailed safety data and the small size of the study, there is very little evidence to conclude that the ingredient can be reasonably expected to be safe for its intended or suggested use.

Overall, the evidence of safety provided for all four of the dietary ingredients submitted is either minimal or lacking. All of the supporting studies were of a short duration, without any evidence demonstrating safety with chronic exposure. You indicated that under conditions of use these ingredients in general, were to be recommended for use in adults (18 and over) and were not to be used by lactating or pregnant women. However, the study exclusion criteria specifically excluded subpopulations with certain medical conditions from the studies. This may be of particular concern, because under your conditions of use you did not indicate any limit or duration of use for the four botanicals and persons excluded from clinical trials are not excluded under your recommended conditions of use.

We have determined that the history of use information you submitted in all four of your notifications has limited utility in evaluating the safety of these ingredients if marketed as

dietary supplements. In conclusion, the information in your notifications does not provide an adequate basis to conclude that *Vitex negundo* L., *Blumea balsamifera* L., *Mormadica charantia* L.- Makiling v., and *Lagerstroemia specious* L. are reasonably expected to be safe when used under the recommended or suggested conditions of use. Therefore, any product containing any of the botanicals listed in your notifications as *Vitex negundo* L., *Blumea balsamifera* L., *Mormadica charantia* L.- Makiling v., and *Lagerstroemia specious* L. may be adulterated under 21 U.S.C. 342(f)(1)(B) as a dietary supplement that contains one or more new dietary ingredients at levels for which there is inadequate information to provide reasonable assurance that they will not present a significant or unreasonable risk of illness or injury. Adulterated or unsafe dietary supplements are prohibited under 21 U.S.C. 331(a) and (v) from being introduced or delivered for introduction into interstate commerce.

Your notifications will be kept confidential for 90 days after the filing date of February 11, 2002. After May 11, 2002, the four notifications will be placed on public display at FDA's Docket Management Branch in docket number 95S-0316. However, any trade secret or otherwise confidential commercial information in the notifications will not be disclosed to the public.

Prior to May 11, 2002, you may wish to identify in writing specifically what information in your notifications you believe is proprietary for FDA's consideration. Nevertheless, our Center's Freedom of Information Officer has the authority to make the final decision about what information in the notifications should be redacted before they are posted at Dockets.

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

Sincerely yours,

Felicia B. Satchell

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

KELATRON CORPORATION
1675 West 2750 South • Ogden, Utah 84401
Phone: 801-394-4558 • Fax: 801-394-4559
Corporate Sales Office Phone: 801-627-3050 • Fax: 801-612-9191
Toll Free: 1-800-201-6896
email: biomin@kelatroncorp.com

Mr. Gary Coody
Office of Nutritional Products
Labeling and Dietary Supplements (HFS-805)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, Md. 20740

Dear Mr. Coody,

In reference to the submission of information on the botanicals trademarked **Biodiamed, Biodiamend Biorenal and Biovitabronch/Biovitaflu** in accordance with the regulation:
TITLE: 21 Food And Drugs
Chapter I – Food and Drug Administration
Dept of Health and Human Services
Part 190 – Dietary Supplements
Subpart B—New Dietary ingredient Notification
Sec. 190.6 Requirement for premarket notification

Please accept the enclosed modified pages which include *Directions* (for use) under the *Condition of use* clause.
Also enclosed are additional materials (clinical trial data)on Biorenal for your review. I believe this was the missing information.

Please call me directly at my office in North Carolina, 252-234-7160 if further information is needed.

Thank you,

Mary Ann Coral-Amasifuen

From:
Mary Ann Coral-Amasifuen
Kelatron Corporation World Headquarters
1675 West 2750 South
Ogden, Utah 8440 Phone (801) 394-4558
Kelatron Corporation Botanical Division
2145 Barefoot Park, SW
Wilson, North Carolina 27893 Phone: (252) 234-7160

To:
Office of Nutritional Products
Labeling and Dietary Supplements (HFS-805)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, Md. 20740
Atten: Gary Coody

In accordance with:
TITLE: 21 Food And Drugs
Chapter I – Food and Drug Administration
Dept of Health and Human Services
Part 190 – Dietary Supplements
Subpart B—New Dietary ingredient Notification
Sec. 190.6 Requirement for premarket notification

(1) **Name and address of distributor**: Kelatron Corporation
1675 West 2750 South
Ogden, Utah 84401
(2) **Name of new dietary ingredient**: BioDiamend (*Lagerstroemia Specious, L*)

(3) **Description of new ingredient;** Biodiamed is the bulk pure leaf powder of the plant *Lagerstroemia Specious*, L. harvested for medicinal purposes in the Philippines. There has been clinical research done on the effectiveness of this plant for lowering blood sugar in mild cases of diabetes mellitus. It is currently in use in the Asian market under the name Banaba which is the local name for the plant in southeast Asia.

(3) (i) **Level of new ingredient**: the product contains only the pure plant leaf powder and no other substance to be sold in bulk powder form to retail manufacturers.

(3) (ii) **Condition of use**: In general, to be used by adults (18 and over). Not to be used by lactating or pregnant women. Directions for use: Prepare water extract of 125 mg of leaf plant powder and drink once per day.

(4) **History of use** *see attachment 4a*

(5) **Signature** _____ **Date** 2.5.02

Received DSLR
2/11/02

RECEIVED
2/11/02

January 18, 2002

Mr. Coody,

I have made corrections to the Conditions of use portion in three of the applications.

We will send the full text article and remaining Condition of use modification when I arrive back to my office in North Carolina.

It would be helpful if you would log in the botanical products that are in compliance with the information requested.

Thank you,

-Mary Ann Cook-Cross

From:
Mary Ann Coral-Amasifuen
Kelatron Corporation World Headquarters
1675 West 2750 South
Ogden, Utah 84401 Phone (801) 394-4558
Kelatron Corporation Botanical Division
2145 Barefoot Park, SW
Wilson, North Carolina 27893 Phone: (252) 234-7160

To:
Office of Nutritional Products
Labeling and Dietary Supplements (HFS-820)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street SW
Washington, DC 20204

In accordance with:
TITLE: 21 Food And Drugs
Chapter I – Food and Drug Administration
Dept of Health and Human Services
Part 190 – Dietary Supplements
Subpart B—New Dietary ingredient Notification
Sec. 190.6 Requirement for premarket notification

(1) **Name and address of distributor**: Kelatron Corporation
1675 West 2750 South
Ogden, Utah 84401

(2) **Name of new dietary ingredient**: BioDiamend (LAGERSTROEMIA SPECIOUS, L.

(3) **Description of new ingredient:** Biodiamend is the bulk pure leaf powder of the plant LAGERSTROEMIA SPECIOUS, L. harvested for medicinal purposes in the Philippines. There has been clinical research done on the effectiveness of this plant for lowering blood sugar. It is currently in use in the Asian market under the name ~~Ampayuka~~ BAU which is the local name for the plant in southeast Asia.

(3) (i) **Level of new ingredient**: the product contains only the pure plant leaf powder and no other substance to be sold in bulk powder form to retail manufacturers.

(3) (ii) **Condition of use**: clinical trials indicated that BioDiamed may have some blood sugar lowering properties in vivo and therefore the recommended use is that it may be helpful for blood sugar regulation and type II Diabetes mellitus.

(4) **History of use**: *see attachment 4A*

(5) **Signature** _____ **Date** 12·18·01

RECEIVED 1/3/02

ATTACH: 9A

Pascual Laboratories, Inc.

PLEASE ADDRESS ALL CORRESPONDEN
TO THE COMPANY AT C.P.O BOX 12
Q.C., PHILIPPINES

Postal Address: C.P.O. Box 1267 Q.C., Philippines

FOUNDED 1946

ATTN : **MR. ROBERT W. WILKINS**
Pacific Rim Nutrition

FROM: **Efren D. Morota**
Pascual Laboratories, Inc.

DATE : June 14, 2000

SUBJ : **TWO PRODUCTS FOR DIABETES**

Please find attached initial articles we have gathered in support of the two herbal plants namely **AMPALAYA & BANABA.**

The Philippine Health Council will finish early next year a Full Technical Study on Ampalaya (similar to Ascof & Re-leaf studies).

For Banaba, we are fortunate to obtain a copy of the Clinical Study made in Japan on the effects of Banaba on mild cases of Diabetes Mellitus.

We are sending along with these information 100 capsules of Ampalaya 500 mg for your perusal. We will also send Banaba Teas once samples are available.

Mr. Wilkins, please let us know how we can be of further service to you.

Respectfully yours,

Efren D. Morota