Robert J. Schoenberg
RIKER DANZIG SCHERER HYLAND & PERRETTI LLP
Headquarters Plaza
One Speedwell Avenue
Morristown, New Jersey 07962-1981
(973) 451-8511
Email: rschoenberg@riker.com

Attorneys for Plaintiff
Everett Laboratories, Inc.

UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

EVERETT LABORATORIES, INC., Plaintiff, v. BRECKENRIDGE PHARMACEUTICAL, INC., Defendant.	Civil Action No. _____ (Related to Civil Action No. 08-3156 (JLL)) Hon. **VERIFIED COMPLAINT AND JURY DEMAND** ***Document Filed Electronically***

Plaintiff Everett Laboratories, Inc. ("Everett"), by its undersigned attorneys, for its Verified Complaint against Defendant Breckenridge Pharmaceutical, Inc. ("Breckenridge" or "Defendant"), alleges as follows:

JURISDICTION AND VENUE

1. This Court has original and exclusive jurisdiction of this action, pursuant to 28 U.S.C. §§ 1331 and 1338(a), because the action arises under the Patent Laws of the United States, Title 35, United States Code. The Court also has original jurisdiction over the unfair competition claim stated herein, pursuant to 28 U.S.C. § 1338(b), because the claim arises under Section 43(a) of the Lanham Act, 15 U.S.C. § 1125(a).

2. This Court also has jurisdiction under 28 U.S.C. § 1332(a)(1) because complete diversity of citizenship exists between the parties and the matter in controversy exceeds the sum

of $75,000, exclusive of interest, costs and attorney's fees.

3. The Court has supplemental jurisdiction, pursuant to 28 U.S.C. § 1367, over the state law claims pled herein.

4. The Court has personal jurisdiction over Defendant in this action because Defendant is a national company that maintains an office in Fairfield, New Jersey and otherwise regularly conducts business in New Jersey. Breckenridge is in the business of selling prescription products to retailers, wholesalers, distributors, and other purchasers of such products nationwide, including New Jersey. Moreover, on information and belief, Breckenridge has offered to sell, offers to sell, and will sell infringing products across the United States and/or indirectly causes others to infringe the patent contributorily or through inducement. Additionally, Defendant has consented to the jurisdiction of the state and federal courts in New Jersey by registering as a foreign corporation with the New Jersey Secretary of State and appointing a registered agent for service of process in this state.

5. This Complaint involves a patented prescription-only nutritional supplement marketed and sold by Plaintiff under the brand name "Strovite® Advance" which Defendant has improperly copied and attempted to market and sell under the name "Nutravance." In so doing, Defendant is, *inter alia*, violating Plaintiff's rights under its lawfully issued patents.

6. In several respects this dispute relates to, and is a continuation of, a very similar pending dispute between Plaintiff and Defendant concerning another prescription-only nutritional supplement product sold by Plaintiff ("Vitafol®-OB") which Defendant improperly copied and attempted to market and sell (under the name "Multifol Plus"). That dispute is currently the subject of the case *Everett Laboratories, Inc. v. Breckenridge Pharmaceutical, Inc.*, Civil Action No. 08-3156 (JLL) (the "Vitafol®-OB Case"), which is pending in this Court before the Honorable Jose L. Linares, U.S.D.J. In August 2008, Judge Linares entered an order

preliminarily enjoining Defendant from marketing and selling Multifol Plus based on Plaintiff's contention that Multifol Plus infringes Plaintiff's patent rights in U.S. Patent Nos. 6,814,983 and 7,390,509. Defendant has appealed the entry of the preliminary injunction and that case remains pending before the U.S. Court of Appeals for the Federal Circuit, *Breckenridge Pharmaceutical, Inc. v. Everett Laboratories, Inc.*, No. 2008-1601 (the "Federal Circuit Appeal"). In the Federal Circuit Appeal, Defendant contends that the patents for Vitafol®-OB are invalid as "obvious."

7. On January 8, 2009, the Office of Mediation for the Federal Circuit convened a mediation session in connection with the Federal Circuit Appeal. However, on the morning of the mediation Plaintiff learned that the prior day -- January 7, 2009 – Breckenridge filed a complaint for declaratory judgment in the United States District Court for the Southern District of Florida, styled *Breckenridge Pharmaceutical, Inc. v. Everett Laboratories, Inc.,* Case No. 09-80015-Civ-MARRA/JOHNSON (the "Florida Complaint"). Breckenridge contends therein, among other things, that certain Everett patents relating to its Strovite® Advance product are invalid, *inter alia*, as obvious under 35 U.S.C. § 103.

8. Both the Vitafol®-OB Case (and the Federal Circuit Appeal) and the Florida Complaint (and this new case) all involve the same principal issue: whether Everett's patents for its prescription-only nutritional supplements are invalid as obvious under 35 U.S.C. § 103.

9. Venue is proper in this judicial district under 28 U.S.C. §§ 1391(b) and 1400(b) because Defendant's unlawful acts of infringement have occurred, and will continue to occur, in this judicial district and Defendant resides in this judicial district.

THE PARTIES

10. Everett is a corporation organized and existing under the laws of the State of New Jersey, having its headquarters and principal place of business at 29 Spring Street, West Orange, New Jersey.

11. On information and belief, Defendant is a corporation organized and existing under the laws of the state of Florida and/or Delaware, having its headquarters and principal place of business at 1141 South Rogers Circle, Suite 3, Boca Raton, Florida, 33487.

12. According to its website (www.bpirx.com), Defendant maintains an office at 1 Passaic Avenue, Fairfield, New Jersey, 07004, with several employees including a Vice President of Sales, a Director of National Accounts, a National Account Manager and a Director of Sales.

PLAINTIFF EVERETT LABORATORIES

13. Everett is a pharmaceutical company that has been and continues to market and sell various prescription-only nutritional supplement products throughout the United States. Everett's reputation has been and continues to be enviable both in the trade and to the general consuming public in the United States. Everett is well known to prescribers of Rx nutritional supplements and medicines as well as to retailers, wholesalers, physicians, pharmacists, patients and distributors in the industry in the United States.

14. Since December 18, 2002, Everett has continuously and actively engaged in selling a nutritional supplement called Strovite® Advance, which was formulated to provide the necessary vitamins, minerals, and other nutrients to individuals in physiologically stressful condition and to minimize the effect of exogenous iron supplementation. It contains specified quantities, or ranges of quantities, of vitamins E, D_3, C, folic acid, B_1, B_2, B_6, B_{12}, carotenoids, niacin; biotin, and pantothenic acid, and minerals magnesium, manganese, zinc, selenium, chromium, and copper, and other nutrients alpha lipoic acid and lutein. *See* Strovite® Advance product insert attached hereto as Exhibit A.

15. Everett has engaged in extensive advertising and promotion of Strovite® Advance to gain goodwill and public recognition of its product. To that end, Everett has spent substantial sums of money and resources to develop, advertise, and market Strovite® Advance.

16. On December 9, 2003, U.S. Patent No. 6,660,293, entitled "Compositions And Methods For Prophylactic and Therapeutic Supplementation of Nutrition in Subjects" ("the '293 Patent"), was duly and validly issued to the inventors John A. Giordano and Charles Balzer. A true and correct copy of U.S. Patent No. 6,660,293 is attached hereto as Exhibit B. Everett is the owner by assignment of the '293 Patent.

17. The '293 Patent is directed to compositions and methods for therapeutic nutritional supplementation of subjects in physiologically stressful states, including but not limited to individuals suffering from obesity, hypertension, heart failure, anorexia, alcoholism and other diseases. Claims of the '293 Patent cover Everett's Strovite® Advance prescription multivitamin product.

18. On March 8, 2005, U.S. Patent No. 6,863,904, entitled "Compositions And Methods For Prophylactic and Therapeutic Supplementation of Nutrition in Subjects" ("the '904 Patent"), was duly and validly issued to the inventors John A. Giordano and Charles Balzer. A true and correct copy of U.S. Patent No. 6,863,904 is attached hereto as Exhibit C. Everett is the owner by assignment of the '904 Patent.

19. The '904 Patent is directed to compositions and methods for nutritional supplementation of subjects in physiologically stressful states, including but not limited to individuals suffering from obesity, hypertension, heart failure, anorexia, alcoholism and other diseases. Claims of the '904 Patent cover Everett's Strovite® Advance prescription multivitamin product.

20. At all times prior to and since issuance of the '293 Patent and '904 Patent, Everett has marked its applicable products, including its patented Strovite® Advance prescription multivitamin product containing the vitamins and minerals claimed in the patents-in-suit, with "Patent Pending" or the '293 Patent number and '904 Patent number, providing constructive notice to the public and Defendant. *See* Strovite® Advance product packaging attached hereto as Exhibit A.

DEFENDANT BRECKENRIDGE PHARMACEUTICAL
AND ITS ILLEGAL CONDUCT

21. Upon information and belief, Breckenridge markets, offers for sale and/or sells in the United States "Nutravance," a lower cost vitamin and mineral supplement that is identical to Everett's Strovite® Advance brand product and which infringes at least one claim of the '293 and '904 Patents. Like Everett's patented Strovite® Advance product, Nutravance is a prescription vitamin and mineral supplement specially formulated therapeutic nutritional supplementation.

22. Everett is informed and believes, and on that basis alleges, that Defendant intentionally copied the formulation of Everett's established patented Strovite® Advance brand product for use in Defendant's lower cost Nutravance product. Indeed, Defendant's Nutravance product contains the exact same vitamins, minerals, and other nutrients, in the exact same amounts, as that contained in Everett's established patented Strovite® Advance brand product.

23. Everett is informed and believes, and on that basis alleges, that Defendant's intentional and illegal conduct was part of a calculated plan to improperly benefit from Everett's efforts and directly, deliberately, and unfairly compete with Everett's established patented Strovite® Advance brand product.

24. Everett is informed and believes, and on that basis alleges, that Defendant has spent relatively little money or resources, if any, developing the Nutravance product formulation, and instead, intentionally copied Everett's proprietary patented Strovite® Advance formulation, for use in direct, deliberate, and unfair competition with Everett's established patented Strovite® Advance brand product.

25. Everett is informed and believes, and on that basis alleges, that because of Defendant's use, advertising, marketing, and offering for sale identical lower cost products of Everett's established patented Strovite® Advance brand product, Everett will suffer damage and losses, including but not limited to irreparable injury to its business reputation and goodwill. Indeed every sale of Defendant's lower cost Nutravance product is a sale lost by Everett of its established patented Strovite® Advance brand product.

THE FLORIDA COMPLAINT

26. Breckenridge filed the Florida Complaint on January 7, 2009, the day before its scheduled mediation with Everett in the Federal Circuit Appeal and the day it began to market and offer for sale its Nutravance product.

27. Prior to obtaining a copy of the already filed Florida Complaint, Everett had no knowledge of the Nutravance product, had not engaged in any communications with Breckenridge concerning the Nutravance product, had not seen or evaluated the Nutravance product and had not taken any steps to restrain or interfere with Breckenridge's right to market the Nutravance product. Accordingly, Everett had no plans or intention, immediate or otherwise, of initiating a lawsuit alleging that Breckenridge's marketing or sale of Nutravance infringed either the '904 Patent or the '293 Patent.

28. At the time Breckenridge filed the Florida Complaint there was no substantial controversy between the parties of sufficient immediacy and reality to warrant the issuance of a declaratory judgment.

FIRST CLAIM FOR RELIEF

(Infringement of U.S. Patent No. 6,660,293)

29. The allegations of paragraphs 1-28 above are hereby re-alleged and incorporated herein by reference.

30. Everett is the owner, by assignment, of the '293 Patent. The '293 Patent was duly and legally issued by the PTO on December 9, 2003.

31. Upon information and belief, Defendant has through the conduct described above, engaged in the marketing, sale, and offer for sale of products that infringed and continue to infringe, directly and/or indirectly by contributorily infringing and/or inducing to infringe, one of more of the claims of Everett's '293 Patent, in violation of 35 U.S.C. § 271 and without Everett's authority. The infringing product embodying the claimed invention(s) is Defendant's Nutravance multivitamin product.

32. Everett is informed and believes, and thereon alleges, that Defendant has engaged in the complained of activities with actual knowledge of the '293 Patent.

33. By reason of Defendant's infringement, Everett has suffered and is suffering damages, including impairment of the value of the '293 Patent, in an amount yet to be determined.

34. Defendant's acts of infringement are causing irreparable harm to Everett and will continue to cause irreparable harm unless enjoined by this Court.

35. Defendant's acts of infringement have been committed with notice and knowledge of Everett's patent rights and, upon information and belief, Defendant's infringement has been willful and carried out without exercising due care.

SECOND CLAIM FOR RELIEF

(Infringement of U.S. Patent No. 6,863,904)

36. Everett realleges and incorporates by reference paragraphs 1-35 as if fully set forth herein.

37. Everett is the owner, by assignment, of the '904 Patent. The '904 Patent was duly and legally issued by the PTO on March 8, 2005.

38. Upon information and belief, through the conduct described above, Defendant has engaged in the marketing, sale, and offer for sale of products that infringed and continue to infringe, directly and/or indirectly by contributorily infringing and/or inducing to infringe, one or more of the claims of Everett's '904 Patent, in violation of 35 U.S.C. § 271 and without Everett's authority. The infringing product embodying the claimed invention(s) is Defendant's Nutravance multivitamin product.

39. By reason of Defendant's infringement, Everett has suffered and is suffering damages, including impairment of the value of the '904 Patent, in an amount yet to be determined.

40. Defendant's acts of infringement are causing irreparable harm to Everett and will continue to cause irreparable harm unless enjoined by this Court.

41. Defendant's acts of infringement have been committed with notice and knowledge of Everett's patent rights and, upon information and belief, Defendant's infringement has been willful and carried out without exercising due care.

THIRD CLAIM FOR RELIEF

(Federal Unfair Competition)

42. Everett realleges and incorporates by reference paragraphs 1 through 41 as if fully set forth herein.

43. Defendant knowingly copied and used the formulations of Everett's established patented Strovite® Advance brand product for its use in advertising, marketing and offering for sale its identical lower cost Nutravance product in the United States.

44. Defendant's actions described above constitute unfair competition in violation of Section 43(a) of the Lanham Act, 15 U.S.C. § 1125(a).

45. The acts of Defendant, and in particular the copying of the formulations for Everett's established patented Strovite® Advance brand product in order to market Defendant's lower cost Nutravance product and to directly compete with Everett, were done by Defendant with the intent to deprive Everett of its property and/or legal rights and/or otherwise to cause injury. Such an unconscionable and deceitful commercial practice justifies an award of punitive and exemplary damages against Defendant.

46. Defendant's misrepresentations concerning the nature, characteristics and/or qualities of its Nutravance product as equivalent to Everett's established Strovite® Advance brand product with the willful and calculated purposes of misleading, deceiving or confusing wholesale distributors, prescribing physicians, dispensing pharmacies and patients are likely to continue unless restrained and enjoined.

47. As a result of Defendant's misrepresentations concerning the nature, characteristics and/or qualities of its Nutravance low cost product in connection with its commercial advertising and promotion, Everett has suffered and will continue to suffer damages and losses including but not limited to, irreparable injury to its business reputation and goodwill.

48. Everett is entitled to injunctive relief and to an order compelling the impounding of all Nutravance products being used, advertised, marketed, offered for sale or distributed by Defendant. Everett has no adequate remedy at law for Defendant's wrongful conduct because, among other things, Everett's intellectual property is unique and valuable property which has no

readily-determinable market value; Defendant's use, advertising, marketing, offering for sale or distribution of its Nutravance product constitutes harm to Everett's business reputation and goodwill such that Everett could not be made whole by any monetary award; and Defendant's wrongful conduct, and the resulting damage to Everett, is continuing.

FOURTH CLAIM FOR RELIEF

(State Law Unfair Competition)

49. Everett realleges and incorporates by reference paragraphs 1 through 48 as if fully set forth herein.

50. This cause of action arises under the New Jersey Fair Trade Act, N.J.S.A. 56:4-1 *et seq.* (2001), and New Jersey common law.

51. Defendant, by reason of the foregoing wrongful acts, has engaged in unfair methods of competition and unfair and deceptive acts and practices in the conduct of its trade, which acts and practices have injured Everett within the meaning, and in violation of, the statutes and common law of the State of New Jersey.

52. The acts of Defendant, and in particular the copying of the formulations for Everett's established patented Strovite® Advance brand product in order to market Defendant's lower cost Nutravance product and to directly compete with Everett, were done by Defendant with the intent to deprive Everett of its property and/or legal rights and/or otherwise to cause injury. Such an unconscionable and deceitful commercial practice justifies an award of punitive and exemplary damages against Defendant.

53. Defendant's wrongful conduct, unless and until enjoined and restrained by order of this Court, will cause great and irreparable injury to Everett in that Defendant's engaging in unfair methods of competition and unfair and deceptive acts and practices has and will continue to harm Everett's goodwill and reputation for which there is no adequate monetary relief.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff Everett Laboratories, Inc. asks that this Court enter judgment against Defendant, granting the following relief:

A. Judgment that Defendant has directly infringed U.S. Patent No. 6,660,293.

B. Judgment that Defendant has directly infringed U.S. Patent No. 6,863,904.

C. Judgment that Defendant has indirectly infringed U.S. Patent No. 6,660,293 by inducing the direct infringement of the '293 Patent.

D. Judgment that Defendant has indirectly infringed U.S. Patent No. 6,863,904 by inducing the direct infringement of the '904 Patent.

E. Judgment that Defendant has indirectly infringed U.S. Patent No. 6,660,293 by contributing to the direct infringement of the '293 Patent.

F. Judgment that Defendant has indirectly infringed U.S. Patent No. 6,683,904 by contributing to the direct infringement of the '904 Patent.

G. That Defendant be held to have willfully engaged in unfair competition in violation of Section 43(a) of the Lanham Act, 15 U.S.C. § 1125(a).

H. That Defendant be held to have engaged in unfair methods of competition and unfair and deceptive acts and practices in violation of N.J.S.A. 56:4-1 and the common law of the State of New Jersey.

I. That a preliminary and permanent injunction issue prohibiting Defendant and their officers, agents, servants, employees, and attorneys, and those persons in active concert or participation with them, from further direct and/or indirect infringement of the '293 and '904 Patents.

J. That the Court enter an order requiring Defendant to:

1. deliver upon oath, to be impounded during the pendency of this action, and for destruction pursuant to judgment herein, all Nutravance products and/or any nutritional supplement that is identical or substantially similar to the patented Strovite® Advance formulations.

2. Place all revenues generated from the sale of Nutravance, as well as all future payments from the sale of Nutravance, in a trust account during the pendency of this action.

K. That Defendant be required to file with the Court and serve on Everett, within 30 days after service of the Court's Order as herein prayed, a report in writing under oath stating in detail the manner and form in which Defendant has complied with the Court's Order.

L. That Defendant be required to account for and pay over to Everett all profits obtained by Defendant from its acts of infringement and for its other violations of law complained of herein.

M. That the Court enter an order declaring that Defendant hold in trust, as constructive trustee for the benefit of Everett, the profits obtained from the distribution of infringing copies of Everett's vitamins, and requiring Defendant to provide Everett a complete accounting of all amounts due and owing to Everett as a result of Defendant's illegal activities.

N. That the Court order Defendant to pay Everett's general, special, actual and statutory damages including, but not limited to, a trebling of Everett's damages, pursuant to N.J.S.A. 56:4-2.

O. That Defendant pay Everett additional damages for willful infringement of the '293 and '904 Patents and other violations of law complained herein, in an amount to be determined at trial, pursuant to 35 U.S.C. § 284.

P. Judgment that this is an exceptional case under 35 U.S.C. § 285 and awarding Everett its costs, expenses and reasonable attorneys' fees incurred in this action.

Q. Such other and further relief as the Court deems just and proper.

DEMAND FOR JURY TRIAL

Pursuant to Rule 38, Fed. R. Civ. P., Plaintiff Everett hereby demands a jury trial on all issues triable of right by a jury.

Respectfully submitted,

RIKER DANZIG SCHERER HYLAND
& PERRETTI LLP
Attorneys for Plaintiff
Everett Laboratories, Inc.

By /s/ Robert J. Schoenberg
ROBERT J. SCHOENBERG

Headquarters Plaza
One Speedwell Avenue
Morristown, New Jersey 07962
Telephone: (973) 538-0800
Facsimile: (973) 451-8604
Email: rschoenberg@riker.com

Dated: January 13, 2009.

Of Counsel:
DON J. PELTO
M. ROY GOLDBERG
SHEPPARD, MULLIN, RICHTER & HAMPTON LLP
1300 I Street, NW, 11th Floor East
Washington, DC 20005
Telephone: (202) 218-0000
Facsimile: (202) 218-0020

CERTIFICATION OF NON-ARBITRABILITY

Pursuant to Local Civil Rule 201.1(d)(2), the undersigned attorneys for Plaintiff, Everett Laboratories, Inc., certify that this action is not eligible for arbitration under Local Civil Rule 201.1 because the relief sought in the Complaint primarily consists of a demand for preliminary and permanent injunctive relief, as well as damages believed to be in excess of $150,000.00, exclusive of interest, costs, and any claim for punitive damages, and involves complex issues of patent law.

LOCAL CIVIL RULE 11.2 CERTIFICATION

Pursuant to L. Civ. R. 11.2, the undersigned attorney for Plaintiff, Everett Laboratories, Inc., certifies as follows: the dispute that is the subject of this Complaint is also the subject of an action filed by Defendant Breckenridge Pharmaceutical, Inc. styled *Breckenridge Pharmaceutical, Inc. v. Everett Laboratories, Inc.*, Case No. 09-80015-Civ-MARRA/JOHNSON (the "Florida Complaint"). In addition, as set forth above, Plaintiff believes that the dispute reflected in the instant Complaint directly relates to, and is a continuation of, the dispute between the parties that exists in the case pending before this Court styled *Everett Laboratories, Inc. v. Breckenridge Pharmaceutical, Inc.*, Civil Action No. 08-3156 (JLL), a portion of which is currently on appeal before the U.S. Court of Appeals for the Federal Circuit, No. 2008-1601. In addition, one of the patents-in-suit, the '983 Patent, was the subject of a similar action filed in this Court by Everett against River's Edge Pharmaceuticals, Inc., Civil Action No. 08-75 (KSH). That case was settled and dismissed in 2008.

RIKER DANZIG SCHERER HYLAND
& PERRETTI LLP
Attorneys for Plaintiff
EVERETT LABORATORIES, INC.

By /s/ Robert J. Schoenberg
ROBERT J. SCHOENBERG

Dated: January 13, 2009

VERIFICATION OF COMPLAINT

I, John A. Giordano, of full age, hereby declare upon my oath, the following:

1. I am an executive Vice President of Everett Laboratories, Inc., plaintiff in the above-captioned lawsuit against defendant Breckenridge Pharmaceutical, Inc.

2. I have read the foregoing Verified Complaint and it is true to the best of my knowledge, except as to matters stated upon information and belief which I believe to be true.

3. I certify that the foregoing statements are true. I am aware that if any of the foregoing statements are willfully false, I am subject to punishment.

JOHN A. GIORDANO

Dated: January 13, 2009

Exhibit A

Strovite® Advance
Product Insert

STROVITE® ADVANCE

STROVITE® ADVANCE

IRON FREE - ANTIOXIDANT - VITAMIN/MINERAL

Each caplet contains:

Fat-soluble Vitamins	
Carotenoids (Alpha-Carotene, Beta-Carotene, Cryptoxanthin, Lutein, Zeaxanthin)	3000 IU
Vitamin E (Succinate)	100 IU
Vitamin D_3	400 IU
Water-soluble Vitamins	
Vitamin C (Ascorbic Acid)	300 mg
Vitamin B_1 (Thiamine HCL)	20 mg
Vitamin B_2 (Riboflavin)	5 mg
Niacin (Niacinamide)	25 mg
Folic Acid	1 mg
Vitamin B_6 (Pyridoxine HCL)	25 mg
Biotin	100 mcg
Pantothenic Acid (Calcium Pantothenate)	15 mg
Vitamin B_{12} (Cyanocobalamin)	50 mcg
Minerals	
Magnesium (Magnesium Oxide)	50 mg
Manganese (Manganese Sulfate)	1.5 mg
Zinc (Zinc Oxide)	25 mg
Selenium (Sodium Selenate)	100 mcg
Chromium (Chromic Chloride)	50 mcg
Copper (Cupric Sulfate)	1.5 mg
Other Nutrients	
Alpha Lipoic Acid	15 mg
Lutein	5 mg

Other ingredients: Dicalcium Phosphate, Microcrystalline Cellulose, Stearic Acid, Croscarmellose Sodium, Magnesium Stearate, Polyvinylpyrrolidone, Hydroxypropylmethylcellulose, Titanium Dioxide, Magnesium Silicate, Polyethylene Glycol, Mineral Oil, Methocel, and Sodium Lauryl Sulfate.

DESCRIPTION:

STROVITE® ADVANCE is a prescription-only multivitamin/mineral caplet specially formulated for prophylactic or therapeutic nutritional supplementation in physiologically stressful conditions.

STROVITE® ADVANCE supplies therapeutic levels of water soluble vitamins (ascorbic acid, folic acid, vitamins: B_1, B_6, B_{12}); supplemental levels of vitamin B_2, niacin, biotin, pantothenic acid, fat soluble nutrients, mixed carotenoids, vitamins E and D. Minerals (chromium, magnesium, manganese, selenium, zinc, copper). Also contained in **STROVITE® ADVANCE** are the nutrients alpha-lipoic acid and lutein.

Recent medical reports have shown a causal effect regarding the use of folic acid and the lowering of elevated levels of homocysteine. Elevated homocysteine levels have been identified as one of the risk factors for heart attacks and strokes in men.

INDICATIONS AND USAGE:

STROVITE® ADVANCE is indicated for prophylactic or therapeutic conditions. These include:

Conditions causing depletion, or reduced absorption or bioavailability of essential vitamins and minerals.

Inadequate intake due to highly restricted or unbalanced diets such as those frequently associated with anorexic conditions and other states of severe malnutrition.

Gastrointestinal disorders, chronic alcoholism, chronic or acute infections (especially those involving febrile illness), prolonged or wasting disease, congestive heart failure, hyperthyroidism, poorly controlled diabetes or other physiologic stress.

Also patients on estrogenic oral contraceptives or other estrogen therapy, antibacterials which affect intestinal microflora, or other interfering drugs.

Certain conditions resulting from severe B-vitamin or ascorbic acid deficiency.

Cheilosis, gingivitis, stomatitis and certain other classic water-soluble vitamin deficiency syndromes.

Conditions resulting in increased needs for essential vitamins and minerals.

Recovery from surgery or trauma involving severe burns, fractures or other extensive tissue damage. In addition, pregnant women and those with heavy menstrual bleeding.

CONTRAINDICATIONS:

STROVITE® ADVANCE is contraindicated in patients with hypersensitivity to any of its components.

Not intended for treatment of pernicious anemia or other megaloblastic anemias where vitamin B_{12} is deficient. Neurologic involvement may develop or progress, despite temporary remission of anemia, in patients with vitamin B_{12} deficiency who receive supplemental folic acid and who are inadequately treated with B_{12}.

Drug Treatment and Interactions:

As little as 5 mg of Pyridoxine daily can decrease the efficacy of Levodopa in the treatment of Parkinsonism. Therefore, **STROVITE® ADVANCE** is not recommended for patients undergoing such therapy.

ADVERSE REACTIONS:

Adverse reactions have been reported with specific vitamins and minerals, but generally at levels substantially higher than those in **STROVITE® ADVANCE**. However, allergic and idiosyncratic reactions are possible at lower levels. Iron, even at the usual recommended levels, has been associated with gastrointestinal intolerance in some patients.

DOSAGE AND ADMINISTRATION:

Usual adult dosage: one caplet daily.

HOW SUPPLIED:

White, oblong caplets; embossed **EV 0208; NDC # 0642-0208-10**
Bottles of 100 Caplets

Store at controlled room temperature, 15-30°C (59-86°F). Avoid excessive heat. Protect from light and moisture.

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

Keep out of reach of children.

R_x Only

MANUFACTURED FOR:
EVERETT LABORATORIES, INC.
West Orange, NJ 07052

MANUFACTURED BY:
CONTRACT PHARMACAL CORP.
Hauppauge, NY 11788

U.S. PATENT NO. 6,660,293

N 3 06420 20810 2

Exhibit B

U.S. Patent No. 6,660,293

US006660293B2

(12) **United States Patent**
Giordano et al.

(10) **Patent No.: US 6,660,293 B2**
(45) **Date of Patent: Dec. 9, 2003**

(54) **COMPOSITIONS AND METHODS FOR PROPHYLACTIC AND THERAPEUTIC SUPPLEMENTATION OF NUTRITION IN SUBJECTS**

(75) Inventors: **John A. Giordano**, West Orange, NJ (US); **Charles Balzer**, Lavalette, NJ (US)

(73) Assignee: **Everett Laboratories, Inc.**, West Orange, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/982,205**

(22) Filed: **Oct. 19, 2001**

(65) **Prior Publication Data**

US 2003/0012826 A1 Jan. 16, 2003

Related U.S. Application Data

(60) Provisional application No. 60/301,443, filed on Jun. 29, 2001.

(51) **Int. Cl.**[7] **A61K 47/00**

(52) **U.S. Cl.** **424/439**; 424/400; 424/451; 424/464; 424/489

(58) **Field of Search** 424/400, 439, 424/451, 464, 489

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Primary Examiner—Thurman K. Page
Assistant Examiner—Charesse Evans
(74) *Attorney, Agent, or Firm*—Preston Gates Ellis & Rouvelas Meeds LLP

(57) **ABSTRACT**

The present invention relates to compositions without added iron and methods for prophylactic nutritional supplementation and therapeutic nutritional supplementation. Specifically, the method involves administering to an individual a composition comprising carotenoids, vitamin E, vitamin D, vitamin C, thiamine, riboflavin, niacin, folic acid, pyridoxine, biotin, pantothenic acid, cobalamin, magnesium, manganese, zinc, selenium, chromium, copper, alpha lipoic acid, and lutein, wherein the composition is free of added iron.

84 Claims, No Drawings

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COMPOSITIONS AND METHODS FOR PROPHYLACTIC AND THERAPEUTIC SUPPLEMENTATION OF NUTRITION IN SUBJECTS

CROSS REFERENCE TO RELATED APPLICATION

The present invention is related to and, in accordance with the provisions of 35 U.S.C. §119(e), claims the benefit of provisional patent application Serial No. 60/301,443 filed Jun. 29, 2001, which is expressly incorporated fully herein by reference.

FIELD OF THE INVENTION

The present invention relates to compositions comprising various vitamins and minerals, and without added iron, and methods for using these compositions for prophylactic nutritional supplementation and therapeutic nutritional supplementation in, for example, physiologically stressful conditions and to minimize the effect of exogenous iron supplementation.

BACKGROUND OF THE INVENTION

Nutrition plays a critical role in maintaining good health. Proper nutrition prevents dietary deficiencies, and also protects against the development of disease. Proper nutrition plays an increasingly important role as the body faces physiological stress. For example, as the body ages it suffers significant physiological stresses. Specifically, as the body metabolism shifts to accumulating larger fat stores and decreasing lean body mass, this increase in body weight may lead to obesity and associated conditions such as diabetes, cardiovascular disease, hypertension, osteoarthritis, and cancer. Other conditions, such as anorexia, malnutrition, gastrointestinal disorders, chronic alcoholism, chronic infections, acute infections, congestive heart failure, hyperthyroidism, poorly controlled diabetes, cheilosis, gingivitis, stomatitis and dietary restrictions, often result in physiological stresses that may be exacerbated by poor nutrition. In particular, these disease states may result in increased oxidative stress or elevated homocysteine levels that further compromise health.

Thus, nutritional supplementation serves a vital role in protecting against poor nutrition and disease. More specifically, nutritional supplementation may provide the necessary vitamins, minerals, and other nutrients that might otherwise be lacking in the diet, and provide the nutritional defense against disease development. The invention herein provides for compositions and methods, specifically using an iron-free multi-vitamin/mineral/antioxidant formulation, designed to optimize health and wellness, minimize oxidative stress, and normalize homocysteine levels.

SUMMARY OF THE INVENTION

The present invention provides nutritional compositions without iron and methods of using these compositions for both prophylactic and therapeutic nutritional supplementation, specifically in physiologically stressful conditions. Specifically, the present invention relates to novel compositions of vitamins and minerals, without exogenous iron, that can be used to supplement the nutritional deficiencies observed in patients with anorexia, malnutrition, gastrointestinal disorders, chronic alcoholism, chronic infections, acute infections, congestive heart failure, hyperthyroidism, poorly controlled diabetes, cheilosis, gingivitis, stomatitis, and/or dietary restrictions. In addition, the compositions may be used to treat the nutritional deficiencies of patients suffering from a disease state that results in increased oxidative stress or elevated homocysteine levels.

The compositions of the present invention include various vitamins and minerals that improve the nutritional state of a patient; these compositions preferably may be used therapeutically or prophylacticly. The vitamins of the present invention may preferably comprise one or more of carotenoids, vitamin E, vitamin D_3, vitamin C, thiamine, riboflavin, niacin, folic acid, pyridoxine, biotin, pantothenic acid, and cyanocobalamin. The minerals of the present invention may preferably include one or more of magnesium, manganese, zinc, selenium, chromium, and copper. In addition, the present invention may preferably comprise other nutritional elements, such as alpha lipoic acid, and/or lutein. The compositions of the present invention preferably do not include exogenous iron as an added component.

In a preferred embodiment, the compositions of the present invention comprise carotenoids in a range of about 2400 IU to about 3600 IU, vitamin E in a range of about 80 IU to 120 IU, vitamin D in a range of about 320 IU to about 480 IU, vitamin C in a range of about 240 mg to 360 mg, thiamine in a range of about 16 mg to 24 mg, riboflavin in a range of about 4 mg to about 6 mg, niacin in a range of about 20 mg to about 30 mg, folic acid in a range of about 0.8 mg to 1 mg, pyridoxine provided in a range of about 20 mg to 30 mg, biotin in a range of about 80 μg to about 120 μg, pantothenic acid in a range of about 12 mg to about 18 mg, cobalamin in a range of about 40 μg to about 60 μg, magnesium in a range of about 40 mg to about 60 mg, manganese in a range of about 1.2 mg to about 1.8 mg, zinc in a range of about 20 mg to about 30 mg, selenium in a range of about 80 μg to 120 μg, chromium in a range of about 40 μg to about 60 μg, copper in a range of about 1.2 mg to about 1.8 mg copper, lipoic acid in a range of about 12 mg to about 18 mg, and lutein in a range from about 4 mg to 6 mg, wherein these compositions are free of added iron.

In another embodiment of the compositions of the present invention, vitamin E is present as d-alpha tocopheryl succinate, vitamin D is vitamin D_3, niacin is niacinamide, chromium is chromium chloride, selenium is present as sodium selenate, zinc is zinc oxide, carotenoids consist of alpha-carotene, beta-carotene, cryptoxanthin, lutein and zeaxanthin, magnesium is magnesium oxide, manganese is present as manganese sulfate, and copper is cupric sulfate.

In a further preferred embodiment of the present invention, the composition includes about 3000 IU carotenoids, about 100 IU d-alpha tocopheryl succinate, about 400 IU vitamin D_3, about 300 mg vitamin C, about 20 mg thiamine, about 5 mg riboflavin, about 25 mg niacinamide, about 1.0 mg folic acid, about 25 mg pyridoxine HCl, about 100 μg biotin, about 15 mg calcium pantothenate, about 50 μg cyanocobalamin, about 50 mg magnesium oxide, about 1.5 mg manganese sulfate, about 25 mg zinc oxide, about 100 μg selenium, about 50 μg chromium chloride, about 1.5 mg cupric sulfate, about 15 mg alpha lipoic acid, and about 5 mg lutein, wherein this composition is free of added iron.

In addition, the compositions of the present invention may be administered to an individual on a daily basis and the composition may be administered orally. Furthermore, the compositions of the present invention may include a pharmaceutically acceptable carrier.

The present invention also relates to methods for supplementing nutritional deficiencies in a patient or person by administering a composition comprising carotenoids, vitamin E, vitamin D, vitamin C, thiamine, riboflavin, niacin, folic acid, pyridoxine, biotin, pantothenic acid, cobalamin, magnesium, manganese, zinc, selenium, chromium, copper, alpha lipoic acid, and lutein, wherein this composition is free of added iron.

The methods of the present invention may be used to treat patients suffering from anorexia, malnutrition, gastrointestinal disorders, chronic alcoholism, chronic infections, acute infections, congestive heart failure, hyperthyroidism, poorly controlled diabetes, cheilosis, gingivitis, stomatitis, and dietary restrictions. In addition, these methods may be used to treat the nutritional deficiencies in patients suffering from a disease state that results in increased oxidative stress or elevated homocysteine levels.

In a preferred embodiment, the methods of the present invention utilize compositions comprising carotenoids in a range of about 2400 IU to about 3600 IU, vitamin E in a range of about 80 IU to about 120 IU, vitamin D in a range of about 320 IU to about 480 IU, vitamin C in a range of about 240 mg to 360 mg, thiamine in a range of about 16 mg to about 24 mg, riboflavin in a range of about 4 mg to about 6 mg, niacin in a range of about 20 mg to about 30 mg, folic acid in a range of about 0.8 mg to about 1 mg, pyridoxine provided in a range of about 20 mg to about 30 mg, biotin in a range of about 80 μg to about 120 μg, pantothenic acid in a range of about 12 mg to about 18 mg, cobalamin in a range of about 40 μg to about 60 μg, magnesium in a range of about 40 mg to about 60 mg, manganese in a range of about 1.2 mg to about 1.8 mg, zinc in a range of about 20 mg to about 30 mg, selenium in a range of about 80 μg to about 120 μg, chromium in a range of about 40 μg to about 60 μg, copper in a range of about 1.2 mg to about 1.8 mg copper, lipoic acid in a range of about 12 mg to about 18 mg, and lutein in a range from about 4 mg to about 6 mg, wherein these compositions are free of added iron.

In a further preferred embodiment, the methods of the present invention utilize a composition comprising about 3000 IU carotenoids, about 100 IU d-alpha tocopheryl succinate, about 400 IU vitamin D_3, about 300 mg vitamin C, about 20 mg thiamine, about 5 mg riboflavin, about 25 mg niacinamide, about 1.0 mg folic acid, about 25 mg pyridoxine HCl, about 100 μg biotin, about 15 mg calcium pantothenate, about 50 μg cyanocobalamin, about 50 mg magnesium oxide, about 1.5 mg manganese sulfate, about 25 mg zinc oxide, about 100 μg selenium, about 50 μg chromium chloride, about 1.5 mg cupric sulfate, about 15 mg alpha lipoic acid, and about 5 mg lutein, wherein this composition is free of added iron.

DETAILED DESCRIPTION

Proper nutrition is essential for maintaining health and preventing diseases. The compositions and methods of the present invention provide the means to optimize good health by utilizing vitamin, mineral, and antioxidant nutritional supplementation. More specifically, the compositions of the present invention contain a variety of antioxidants, which may minimize free radical concentrations and minimize the deleterious effects of oxidative stress, and vitamins and minerals that support normal levels of homocysteine. It is to be understood that the terminology used herein is used for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention. It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise.

The compositions of the present invention may preferably comprise antioxidant factors that may protect against oxidative stress. Oxidative stress occurs as the body's natural use of oxygen creates unstable molecules known as free radicals, which steal stable electron partners from other molecules, launching more free radicals and increased molecular and cellular instability. This 'oxidative stress' is implicated in over 200 diseases, including cardiovascular disease and cancer, which are attributed to free radical oxidation. Rock et al., 96 J. AM. DIETARY ASSOC. 693–702 (1996). For example, lipid peroxidation is the initiating step in the oxidation of low-density lipoproteins (LDL). In turn, the lipid peroxides oxidate other lipoproteins, which are taken up by the cells of the arterial wall. Eventually, the deposited oxidized lipoproteins form an atherosclerotic plaque. Id. The antioxidant components of the compositions and methods described herein may preferably include one or more of vitamin E, selenium, vitamin C, carotenoids, lutein, and lipoic acid.

The compositions and methods of the present invention also may preferably include B-complex vitamins, which are critical for health as each is part of one or more coenzymes in metabolizing food properly. This class of vitamins is water-soluble nutrients, not stored significantly in the body. Importantly, the B-complex vitamins may help normalize homocysteine levels and metabolism. High homocysteine levels have been correlated directly with increased risk of atherosclerosis and other heart disease. Although the exact mechanism by which homocysteine contributes to heart disease is not fully understood, it may act as an endothelial irritant that promotes atherosclerosis by inducing endothelial dysfunction. B-complex vitamins are required for the proper function of the homocysteine metabolic pathway, thus maintaining adequate levels of these vitamins may assist in normalizing homocysteine levels and maintaining good health. The B-complex vitamins of the present compositions and methods may preferably include one or more of thiamin (B_1), riboflavin (B_2), niacin (B_3), pantothenic acid, biotin, folic acid, pyridoxine (B_6) and cobalamin (B_{12}).

Minerals are inorganic, or non-carbon-containing, elements that are critical for healthy physiological processes, and are contemplated in the compositions and methods of the present invention. For example, minerals act as cofactors for hundreds of enzymes that range from those associated, for example, with food digestion, nucleic acid production, protein synthesis to antioxidant enzymes. One particular mineral, chromium, is essential in healthy insulin function, as it plays a direct role in insulin's interactions at the cellular level. The minerals of the compositions and methods of the present invention may preferably include one or more of chromium, zinc, copper, magnesium, and manganese.

Another mineral, iron, is specifically excluded from the compositions and methods of the present invention. Although iron is an essential mineral with many functions, iron has also been implicated as a catalyst for lipid oxidation. Specifically, lipid oxidation associated with LDL cholesterol has been correlated strongly with an increased risk of cardiovascular disease. Moreover, some older patients exhibit sensitivity to iron or build-up of iron concentration in the liver. Although iron supplementation may be indicated in specific population groups or disease states, universal supplementation may not always be recommended. Hence, the compositions and methods of the present invention are preferably free of added iron.

Vitamin D may preferably be a component of the compositions and methods of the present invention. Vitamin D is

a fat-soluble "hormone like" substance essential for healthy bones. This vitamin increases the absorption of calcium and phosphorous from the gastrointestinal tract, and improves essential mineral resorption into bone tissue. Vitamin D can be converted to its active form from exposure of the skin to sunlight. This fact is among the reasons why vitamin D deficiency is common in the elderly, notably the institutionalized, who spend little or no time out of doors. Deficiencies lead to increased bone turnover and loss, and when severe, osteomalacia or softening of the bones. Supplementation with vitamin D has been shown to moderately reduce bone loss, increase serum 25-hydroxyvitamin D, and decrease serum parathyroid hormone levels. Dawson-Hughes et al., 337 NEW ENG. J. MED. 670–76 (1997); Lips et al., 86 J. CLIN. ENDOCRINOL. METAB. 1212–21 (2001).

Preferably, the vitamin D of the compositions and methods of the present invention is vitamin D_3. In the body, vitamin D_3 is produced when its precursor is exposed to ultraviolet irradiation (e.g., sunlight) and then hydroxylated in the liver to form 25-hydroxyvitamin D_3, the major form of vitamin D in the circulation. This form of the vitamin may be hydroxylated again in the kidney, yielding 1,25 hydroxyvitamin D_3, the most potent form of vitamin D. As noted above, vitamin D_3 plays a role in the maintenance of calcium and phosphorus homeostasis, but it is also active in cell differentiation and immune function. In a preferred embodiment of the invention, vitamin D_3 is present in the amount ranging from about 320 IU to about 480 IU. In a particularly preferred embodiment, vitamin D_3 is present in an amount of about 400 IU.

As discussed previously, the antioxidant components of the compositions and methods described herein preferably include vitamin E, selenium, vitamin C, carotenoids, lutein, and lipoic acid.

Vitamin E is a fat-soluble vitamin antioxidant found in biological membranes where it protects the phospholipid membrane from oxidative stress. More specifically, alpha-tocopherol, the most abundant and most active form of the vitamin E family, is the principle lipid-soluble, chain breaking antioxidant in tissue and plasma. RECOMMENDED DIETARY ALLOWANCES 99–101 (Nat'l Research Council, 10th ed., 1989) (hereinafter "RDA"). Vitamin E inhibits the oxidation of unsaturated fatty acids by trapping peroxyl free radicals. It is also an antiatherogenic agent, and studies have demonstrated a reduced risk of coronary heart disease with increased intake of vitamin E. Stampfer et al., 328 New Eng. J. MED. 1444–49 (1993). Vitamin E is available in various forms known to those of skill in the art. In a preferred embodiment of the present invention, vitamin E is present in an amount ranging from about 80 IU to about 120 IU. In a particularly preferred embodiment of the invention, vitamin E is present d-alpha tocopheryl succinate. A preferred embodiment of the invention includes about 100 IU d-alpha tocopheryl succinate.

Along with vitamin E, the mineral selenium is a component of the antioxidant enzyme, glutathione peroxidase, which plays a critical role in the control of oxygen metabolism, particularly catalyzing the breakdown of hydrogen peroxide. Burk, 3 ANN. REV. NUTRITION 53–70 (1983). Glutathione peroxidase prevents the generation of free radicals and decreases the risk of oxidative damage to numerous tissues, including the vascular system. Holben, 99 J. AM. DIETARY Assoc. 836–43 (1999). Another selenoprotein is the enzyme iodothyronine 5'-diodinase that converts thyroxine (T_4) to triiodothyronine (T_3). Selenium is available in many forms known to those of ordinary skill in the art. In a preferred embodiment of the present invention, selenium is included in a range of about 80 μg to about 120 μg. In a preferred embodiment of the invention, selenium is present as sodium selenate. A preferred embodiment of the invention includes about 100 μg sodium selenate.

Vitamin C (also known as ascorbic acid) is another antioxidant present in the invention described herein. The major biochemical role of the water-soluble vitamin C is as a co-substrate in metal catalyzed hydroxylations, and it has antioxidant properties in interacting directly with superoxide hydroxyl radicals and singlet oxygen. Vitamin C also provides antioxidant protection for folate and vitamin E, keeping vitamin E in its most potent form. It also enhances the absorption of iron. RDA, at 115. In addition, vitamin C is required for collagen synthesis, epinephrine synthesis, and bile acid formation. Moreover, vitamin C has been implicated in inhibiting atherosclerosis by being present in extracellular fluid of the arterial wall and potentiating nitric oxide activity, thus normalizing vascular function. A preferred embodiment of the compositions of the present invention includes a supplemental dose of vitamin C, preferably in the amount of about 240 mg to about 360 mg. A preferred embodiment of the present invention includes about 300 mg of vitamin C.

Along with vitamins E and C, and selenium, carotenoids are a group of antioxidants embodied in the present invention. There are over 600 carotenoids occurring naturally in fruits and vegetables. Many of these fat-soluble compounds, of which beta-carotene is a well-known example, have pro-vitamin A activity as well as antioxidant activity. Less-known carotenoids include alpha-carotene, lutein, cryptoxanthine, and zeaxanthin. The compositions and methods herein include a cartonoid complex that closely mirrors that found naturally in fruits and vegetables. In particular, the carotenoids of the present invention may preferably include alpha-carotene, beta-carotene, cryptoxanthin, lutein, and zeaxanthin. In particular, lutein and zeaxanthin are the major carotenoids that make up the macular pigment of the eye's retina, and their antioxidant properties protect the eye from light-induced damage and macular degeneration. Berendschot et al., 41 INVEST. OPHTHALMOL. VIS. SCI. 3322–26 (2000). In a preferred embodiment of the invention, carotenoids are included in a range of about 2400 IU to about 3600 IU. In a more preferred embodiment of the invention, the carotenoids include a mixture of alpha-carotene, beta-carotene, cryptoxanthin, lutein, and zeaxanthin. A preferred embodiment of the invention includes about 3000 IU of a mixture of alpha-carotene, beta-carotene, cryptoxanthin, lutein, and zeaxanthin.

Lutein is also preferably included in the compositions and methods described herein and is preferably included in an amount distinguished from that included in the mixed carotenoids. Regarding the antioxidant activity of lutein, scientists have demonstrated that lutein is an effective antioxidant capable of scavenging peroxyl radicals and quenching reactive oxygen species. Rapp et al., 41 INVEST. OPHTHALMOL. VIS. SCI. 1200–09 (2000). Thus, the compositions and methods of the present invention may include lutein, preferably in the amount ranging from about 4 mg to about 6 mg. A preferred embodiment of the invention comprise about 5 mg lutein.

Lipoic acid is an antioxidant and is preferably included in the compositions and methods of the present invention. Known as the "universal antioxidant," alpha lipoic acid is both a lipid- and water-soluble antioxidant that works synergistically with other antioxidants in the cell's mitochon-

dria. In addition to working with other antioxidant nutrients, lipoic acid has powerful, pro-antioxidant enzyme properties. Alpha lipoic acid is also a cofactor for several regulatory enzymes, including pyruvate dehydrogenase, and appears to have an effect on glucose transport and utilization. Rudich et al., 42 DIABETOLOGIA 949–57 (1999). Alpha lipoic acid also increases tocopherol activity and acts as a metal chelator. Furthermore, alpha lipoic acid improves microvascular perfusion. Haak et al., 108 EXPERIMENTAL & CLINICAL ENDOCRINOLOGY & DIABETES 168–74 (2000). A preferred embodiment of the compositions of the present invention comprises alpha lipoic acid in the amount ranging from about 12 mg to about 18 mg. A particularly preferred embodiment of the present invention comprises about 15 mg of lipoic acid.

In addition to antioxidants, the compositions and methods of the present invention also preferably include one or more B-complex vitamins such as thiamin (B_1), riboflavin (B_2), niacin (B_3), pantothenic acid (B_5), biotin, folic acid, pyridoxine (B_6) and cobalamin (B_{12}).

Thiamine (vitamin B_1) plays a role in carbohydrate metabolism and neural function. It is a coenzyme for the oxidative decarboxylation of alpha-ketoacids (e.g., alpha-ketoglutarate and pyruvate) and for transketolase which is a component of the pentose phosphate pathway. Folate deficiency and malnutrition inhibit the activity of thiamine. RDA, at 123. One embodiment of the compositions of the present invention may comprise thiamine, preferably in the amount ranging from about 16 mg to about 24 mg. In a preferred embodiment of the present invention, the form of thiamine is thiamine HCl. A preferred embodiment of the invention comprises about 20 mg thiamine HCl.

Riboflavin (vitamin B_2) is a component of two flavin coenzymes, flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). These flavoenzymes are involved in a number of oxidation-reduction reactions including the conversion of pyridoxine and niacin. RDA, at 132. Flavoenzymes also play a role in a number of metabolic pathways such as citric acid cycle, amino acid deamination, purine degradation, and fatty acid oxidation and thus help to maintain carbohydrate, amino acid, and lipid metabolism. In one embodiment, the compositions and methods of the present invention comprise riboflavin, preferably in the amount ranging from about 4 mg to about 6 mg. A preferred embodiment of the invention comprises about 5 mg of riboflavin.

Niacin, also called vitamin B_3, is the common name for two compounds: nicotinic acid (also called niacin) and niacinamide (also called nicotinamide). Niacin and is particularly important for maintaining healthy levels and types of fatty acids. Niacin is also required for the synthesis of pyroxidine, riboflavin, and folic acid. RDA, at 137. Administration of niacin may also produce a reduction in total cholesterol, LDL, and very low density lipoprotein (VLDL) levels; and an increase in high density lipoprotein (HDL) cholesterol levels. Nicotinamide adenine dinucleotide (NAD) and NAD phosphate (NADP) are active coenzymes of niacin. These coenzymes are involved in numerous enzymatic reactions such as glycolysis, fatty acid metabolism, and steroid synthesis. Henkin et al., 91 AM. J. MED. 239–46 (1991). One embodiment of the compositions and methods of the present invention may comprise niacin, preferably in the amount ranging from about 20 mg to about 30 mg. In a preferred embodiment of the invention, niacin is present in the form of niacinamide. A preferred embodiment of the invention comprises about 25 mg of niacinamide.

Folic acid (vitamin B_8), also called folate or methylfolate, is essential for the formation of red and white blood cells within bone marrow and also plays a role in heme formation. RDA, at 150. Folic acid in its active form, tetrahydrofolate, is a coenzyme that is involved in the transfer of methyl groups and it plays a role in DNA synthesis, purine synthesis, and amino acid synthesis, such as the conversion of glycine to serine and the transformation of homocysteine to methionine. The activation of folic acid requires a vitamin B_{12}-dependent transmethylation and vitamin B_{12} is also necessary for folic acid delivery to tissues. Id. One embodiment of the compositions and methods of the present invention may comprise folic acid, preferably in the amount ranging from about 0.8 mg to about 1.0 mg. A preferred embodiment of the invention comprises about 1 mg of folic acid.

Pyridoxine (vitamin B_6) is another B-complex vitamin included in the compositions and methods described herein. The administration of pyridoxine may reduce the levels of homocysteine. Bostom et al., 49 KIDNEY INT. 147–52 (1996). The active forms of pyridoxine, pyridoxal-5'-phosphate (PLP) and pyridoxamine-5'-phosphate, are coenzymes for numerous enzymes and as such, are essential for gluconeogenesis, niacin formation, and erythrocyte metabolism. RDA, at 142–143. Pyridoxine is a coenzyme for both cystathionine synthase and cystathionase, enzymes that catalyze the formation of cysteine from methionine. Homocysteine is an intermediate in this process and elevated levels of plasma homocysteine are recognized as a risk factor for vascular disease. Robinson et al., 94 CIRCULATION 2743–48 (1996). Hence, one embodiment of the compositions and methods of the present invention may comprise pyridoxine, preferably in the amount ranging from about 20 mg to about 30 mg. In a preferred embodiment of the invention, pyridoxine is in the form of pyridoxine HCl. A preferred embodiment of the invention comprises about 25 mg pyridoxine HCl.

Biotin, another water-soluble B-complex vitamin, acts a coenzyme for a number of carboxylases, and thus has an important role in gluconeogenesis, fatty acid metabolism, and amino acid metabolism. RDA, at 166. For example, biotin serves as a carboxyl carrier for pyruvate carboxylase, which is involved in gluconeogenesis; acetyl CoA carboxylase, which is involved in fatty acid synthesis; and propionyl-CoA carboxylase, which is involved in glucose production. Researchers believe that biotin inhibits the effects of uremic toxins on tubulin polymerizaton. Braguer et al., 57 NEPHRON 192–96 (1991). Thus, one embodiment of the compositions and methods of the present invention comprises biotin, preferably in the amount ranging from about 80 μg to about 120 μg. A preferred embodiment of the invention comprises about 100 μg biotin.

Pantothenic acid (vitamin B_5) is a component of both the coenzyme A macromolecule and the acyl-carrier protein. These coenzymes function as carriers for acyl groups and are required for the synthesis of fatty acids, cholesterol, steroid hormones, and neurotransmitters. The coenzyme A complex also has a major role in the acetylation and acylation of numerous proteins. RDA, at 169. One embodiment of the compositions and methods of the present invention comprises pantothenic acid, preferably in the amount ranging from about 12 mg to about 18 mg. In a preferred embodiment of the invention, pantothenic acid is present as calcium pantothenate. A preferred embodiment of the invention comprises about 15 mg calcium pantothenate.

Cobalamin (vitamin B_{12}), another important vitamin included in the compositions and methods described herein, can be converted to the active coenzymes, methylcobalamin and 5'-deoxyadenosylcobalamin. These coenzymes are nec-

essary for folic acid metabolism, conversion of coenzyme A, and myelin synthesis. For example, methylcobalamin catalyzes the demethylation of a folate cofactor, which is involved in DNA synthesis. A lack of demethylation may result in folic acid deficiency. RDA, at 159–160. Deoxyadenosylcobalamin is the coenzyme for the conversion of methylmalonyl-CoA to succinyl-CoA, which plays a role in the citric acid cycle. Importantly, cobalamin, along with pyridoxine and folic acid in implicated in the proper metabolism of homocysteine. Cobalamin is available as cyanocobalamin, methylcobalamin, hydroxocobalamin, adenosylcobalamin, and hydroxycyanocobalamin. One embodiment of the compositions and methods of the present invention may comprise cobalamin, preferably in the amount ranging from about 40 μg to about 60 μg. In a preferred embodiment of the invention, cobalamin is present as cyanocobalamin. A preferred embodiment of the invention includes about 50 μg cyanocobalamin.

As noted previously, minerals are inorganic elements that play a crucial role in physiological processes in the body relating to good health. The compositions and methods of the present invention may comprise minerals, and, in a preferred embodiment, comprise one or more of selenium, discussed above, and magnesium, manganese, zinc, chromium, and copper.

Magnesium is found primarily in both bone and muscle. Magnesium is an essential component for over 300 enzymes, including enzymes of biosynthetic pathways, glycolysis, protein synthesis, transketolase reactions, and membrane transport. Magnesium is also involved in the formation of cAMP, a cytosolic second messenger that plays a role in cell signaling mechanisms. In addition, magnesium functions both synergistically and antagonistically with calcium in neuromuscular transmission. RDA, at 188. Specifically, magnesium is critical for the maintenance of electrochemical potentials of nerve and muscle membranes and the neuromuscular junction transmissions, particularly important in the heart. Not surprisingly, magnesium deficiency is tied to cardiovascular disease and hypertension. Agus et al., 17 CRIT. CARE CLINICS 175–87 (2001). Indeed, oral magnesium therapy improves endothelial function in patients with coronary disease. Shechter et al., 102 CIRCULATION 2353–58 (2000). Yet, most individuals in the U.S. receive only about seventy-five percent of the magnesium they need from their diets. Magnesium is available in a variety of salts. One embodiment of the compositions and methods of the present invention comprises magnesium, preferably in the amount ranging from about 40 mg to about 60 mg. In a preferred embodiment of the invention, magnesium is present as magnesium oxide. A preferred embodiment of the invention comprises about 50 mg magnesium oxide.

Manganese, like magnesium, plays a key role in multiple enzymes and is needed for healthy skin, bone, and cartilage formation, as well as glucose tolerance. For example, manganese is a cofactor for enzymes such as glutamine synthetase, pyruvate carboxylase, and mitochrondrial superoxide dismutase. RDA, at 230. In particular, manganese is essential for glycoprotein and proteoglycan synthesis, and thus is involved in the formation of connective and skeletal tissue, as well as carbohydrate and lipid metabolism. It also helps activate superoxide dismutase, an important antioxidant enzyme. Manganese is available in many forms known to those of ordinary skill in the art, including manganese sulfate, manganese oxide, manganese oxy-sulfate, and manganese proteinate. One embodiment of the compositions and methods of the present invention comprises manganese, preferably in the amount ranging from about 1.2 mg to about 1.8 mg. In a preferred embodiment, manganese is present as manganese sulfate. A preferred embodiment of the invention comprises about 1.5 mg of manganese sulfate.

Zinc plays a role in numerous metabolic activities such as nucleic acid production, protein synthesis, and development of the immune system. There are more than 200 zinc metalloenzymes including aldolase, alcohol dehydrogenase, RNA polymerase, and protein kinase C. Zima et al., 17 BLOOD PURIF. 182–86 (1999). Moreover, zinc stabilizes RNA and DNA structures, forms zinc fingers in nuclear receptors, and is a component of chromatin proteins involved in transcription and replication. Zinc is available in many forms, such as zinc oxide and zinc sulfate. One embodiment of the compositions and methods of the present invention comprises zinc, preferably in the amount ranging from about 20 mg to about 30 mg. More preferably, zinc may be present as zinc oxide. A preferred embodiment of the invention comprises about 25 mg zinc oxide.

The trace mineral chromium harmonizes with insulin at the cellular level to optimize the release of energy from glucose, as well as maintaining proper cellular lipid or fat metabolism. Specifically, chromium increases insulin binding to cells, insulin receptor number, and activates the insulin receptor kinase leading to increased insulin sensitivity. Several studies suggest that adequate chromium levels are needed for optimal glycemic control. See, e.g., Anderson et al., 26 DIABETES METABOLABOLISM 22–27 (2000); Vincent, 130 J. NUTRITION 715–18 (2000). The concentration of chromium declines with age, and coronary artery disease appears to be associated with low levels of chromium. RDA, at 241. Yet, ninety percent of adults in the U.S. consume less than the recommended minimum amount of chromium. Chromium is available in various forms known to those skilled in the art, such as chromium chloride, chromium sulfate, chromium potassium sulfate, and chromium picolinate. One embodiment of the compositions and methods of the present invention comprises chromium, preferably in the amount ranging from about 40 μg to about 60 μg. Preferably, chromium is supplied as chromium chloride. A preferred embodiment of the invention comprises 50 μg chromium chloride.

Copper is a component of several enzymes associated with numerous physiological functions, including, for example, oxidase enzymes, such as cytochrome c oxidase, and cytosolic superoxide dismutase. RDA, at 224. In particular, copper is a cofactor of lysyl oxidase, which is critical for lysine cross-linking in collagen and elastin. Copper acts as an antioxidant, and promotes the synthesis of melanin and catecholamines. In addition, copper is present in the blood as ceruloplasmin which is involved in oxidizing iron prior to transport to the plasma. Copper is available in multiple forms, such as cupric oxide, copper sulfate, cupric acetate, and alkaline copper carbonate. One embodiment of the compositions and methods of the present invention comprises copper, preferably in the amount ranging from about 1.2 mg to about 1.8 mg. In a preferred embodiment of the invention, copper comprises cupric sulfate. A preferred embodiment comprises about 1.5 mg cupric sulfate.

The compositions and methods of the present invention represent a combination of essential vitamins and minerals that work together with various metabolic systems and physiological responses of the human body. The active ingredients are available from numerous commercial sources, and in several active forms or salts thereof, known to those of ordinary skill in the art. Hence, the compositions and methods of the present invention are not limited to any

particular form of the vitamin or mineral ingredient described herein.

The ingredients of the present invention are preferably combined into a composition which may be in the form of a solid powder, caplets, tablets, lozenges, pills, capsules, or a liquid, and which may be administered alone or in suitable combination with other components. For example, the composition of the present invention may be administered in one or more caplets or lozenges as practical for ease of administration. Each of the vitamins and minerals is commercially available, and can be blended to form a single composition or can form multiple compositions, which may be co-administered.

To prepare the compositions of the present invention, each of the active ingredients may be combined in intimate admixture with a suitable carrier according to conventional compounding techniques. The carrier may take a wide variety of forms depending upon the form of the preparation desired for administration, e.g., oral, sublingual, nasal, topical patch, or parenteral. Preferably, the composition may consists of one to three caplets or lozenges, the composition of each being identical to each other caplet or lozenge.

In preparing the composition in oral dosage form, any of the usual media may be utilized. For liquid preparations (e.g., suspensions, elixirs, and solutions), media containing, for example water, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used. Carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like may be used to prepare oral solids (e.g., powders, caplets, pills, tablets, capsules, and lozenges). Controlled release forms may also be used. Because of their ease in administration, caplets, tablets, pills, and capsules represent the most advantageous oral dosage unit form, in which case solid carriers are employed. If desired, tablets may be sugar coated or enteric coated by standard techniques. All of these pharmaceutical carriers and formulations are well known to those of ordinary skill in the art. See, e.g., WADE & WALLER, HANDBOOK OF PHARMACEUTICAL EXCIPIENTS (2nd ed. 1994).

Other objectives, features and advantages of the present invention will become apparent from the following specific examples. The specific examples, while indicating specific embodiments of the invention, are provided by way of illustration only. Accordingly, the present invention also includes those various changes and modifications within the spirit and scope of the invention that may become apparent to those skilled in the art from this detailed description. The invention will be further illustrated by the following non-limiting examples.

EXAMPLE 1

A composition of the following formulation was prepared in caplet form, including the appropriate excipients, by standard methods known to those of ordinary skill in the art:

Carotenoids (Alpha-Carotene, Beta-Carotene, Cryptoxanthin, Lutein, Zeaxanthin)	3000 IU
Vitamin E	100 IU
Vitamin D_3	400 IU
Vitamin C (Ascorbic Acid)	300 mg
Vitamin B_1 (Thiamine HCl)	20 mg
Vitamin B_2 (Riboflavin)	5 mg
Niacin (Niacinamide)	25 mg
Folic Acid	1 mg
Vitamin B_6 (Pyridoxine HCl)	25 mg
Biotin	100 μg
Pantothenic Acid (Calcium Pantothenate)	15 mg
Vitamin B_{12} (Cyanocobalamin)	50 μg
Magnesium (Magnesium Oxide)	50 mg
Manganese (Manganese Sulfate)	1.5 mg
Zinc (Zinc Oxide)	25 mg
Selenium (Sodium Selenate)	100 μg
Chromium (Chromium Chloride)	50 μg
Copper (Cupric Sulfate)	1.5 mg
Alpha Lipoic Acid	15 mg
Lutein	5 mg

EXAMPLE 2

A study is undertaken to evaluate the effectiveness of the composition of the present invention in the treatment of patients. The objective of the study is to determine whether oral intake of the composition results in an improvement of the nutritional status of the patient, either therapeutically or prophylactically.

A double-blind, placebo controlled study is conducted over a twelve-month period. A total of sixty subjects (30 men and 30 women), aged 40 to 85 years, suffering from dietary restrictions or a disease state such as anorexia, malnutrition, gastrointestinal disorders, chronic alcoholism, chronic infections, acute infections, congestive heart failure, hyperthyroidism, poorly controlled diabetes, cheilosis, gingivitis, sensitivity to iron, hemosiderosis, hemochromatosis, or stomatitis, or a propensity or disposition to such a disease state are chosen for the study. An initial assessment of nutritional status is conducted utilizing methods such as the peroxide hemolysis test to assess vitamin E deficiency, measurement of erythrocyte transketolase activity to determine thiamine levels, determination of erythrocyte glutathione reductase activity to assess riboflavin status, and high performance liquid chromatography to directly measure PLP and pyridoxine levels.

The sixty subjects are separated into two separate groups of fifteen men and fifteen women. In the first group, each subject is administered 1 to 2 caplets, daily, of the composition as described in Example 1. In the second group (control), each subject is administered 1 to 2 placebo caplets, daily.

An assessment of nutritional status for each subject is measured at one-month intervals for a twelve month period as described above and the data is evaluated using multiple linear regression analysis and a standard students t-test. In each analysis the baseline value of the outcome variable is included in the model as a covariant. Treatment by covariant interaction effects is tested by the method outlined by Weigel & Narvaez, 12 CONTROLLED CLINICAL TRIALS 378–94 (1991). If there are no significant interaction effects, the interaction terms are removed from the model. The regression model assumptions of normality and homogeneity of variance of residuals are evaluated by inspection of the plots of residuals versus predicted values. Detection of the temporal onset of effects is done sequentially by testing for the presence of significant treatment effects at 16, 12, and 8 weeks, proceeding to the earlier time in sequence only when significant effects have been identified at each later time period. Changes from the baseline within each group are evaluated using paired t-tests. In addition, analysis of variance is performed on all baseline measurements and mea-

surable subject characteristics to assess homogeneity between groups. All statistical procedures are conducted using the Statistical Analysis System (SAS Institute Inc., Cary, N.C.). An alpha level of 0.05 is used in all statistical tests.

A statistically significant improvement in the nutritional status is preferably observed in the treated subjects upon completion of the study over the controls. The study may also look at the progression of the disease state, or the prevention or delay of a disease or disease state, or the reduction of the severity of a disease. The differences between nutritional state or the progression of the disease state, or the prevention or delay of a disease or disease state, or the reduction of the severity of a disease, between the treated subjects and controls are preferably statistically significant and or observable by clinical or other tests or evaluations. Therefore, the study confirms that oral administration of the composition of the present invention is effective as a nutritional supplement, either therapeutically or prophylacticly, for example, in preventing the severity or delaying or preventing the onset of a disease.

While there has been described what is presently believed to be the preferred embodiments of the present invention, other and further modifications and changes may be made without departing from the spirit of the invention. All further and other modifications and changes are included that come within the scope of the invention as set forth in the claims. The disclosure of all publications cited above are expressly incorporated by reference in their entireties to the same extent as if each were incorporated by reference individually.

We claim:

1. A composition for supplementing nutritional deficiencies in a patient or person in need thereof, comprising about 2400 IU to about 3600 IU carotenoids, about 80 IU to about 120 IU vitamin E, about 320 IU to about 480 IU vitamin D, about 240 mg to about 360 mg vitamin C, about 16 mg to about 24 mg thiamine, about 4 mg to about 6 mg riboflavin, about 20 mg to about 30 mg niacin, more than 0.8 mg to about 1.2 mg folic acid, about 20 mg to about 30 mg pyridoxine, about 80 μg to about 120 μg biotin, about 12 mg to about 18 mg pantothenic acid, about 40 μg to about 60 μg cobalamin, about 40 mg to about 60 mg magnesium, about 1.2 mg to about 1.8 mg manganese, about 20 mg to about 30 mg zinc, about 80 μg to about 120 μg selenium, about 40 μg to about 60 μg chromium, about 1.2 mg to about 1.8 mg copper, about 12 mg to about 18 mg alpha lipoic acid, and about 4 mg to about 6 mg lutein; wherein said composition is free of added iron.

2. The composition of claim **1**, wherein said composition comprises about 3000 IU carotenoids, about 100 IU vitamin E, about 400 IU vitamin D, about 300 mg vitamin C, about 20 mg thiamine, about 5 mg riboflavin, about 25 mg niacin, about 1.0 mg folic acid, about 25 mg pyridoxine, about 100 μg biotin, about 15 mg pantothenic acid, about 50 μg cyanocobalamin, about 50 mg magnesium, about 1.5 mg manganese, about 25 mg zinc, about 100 μg selenium, about 50 μg chromium, about 1.5 mg copper, about 15 mg alpha lipoic acid, and about 5 mg lutein.

3. The composition of claim **1**, wherein said composition is administered to said patient daily.

4. The composition of claim **1**, wherein said composition is administered to said patient orally.

5. The composition of claim **1**, wherein said composition further comprises a pharmaceutically acceptable carrier.

6. A method for supplementing nutritional deficiencies in a patient or person in need thereof, comprising administering to a patient or a person a composition comprising about 2400 IU to about 3600 IU carotenoids, about 80 IU to about 120 IU vitamin E, about 320 IU to about 480 IU vitamin D, about 240 mg to about 360 mg vitamin C, about 16 mg to about 24 mg thiamine, about 4 mg to about 6 mg riboflavin, about 20 mg to about 30 mg niacin, more than 0.8 mg to about 1.2 mg folic acid, about 20 mg to about 30 mg pyridoxine, about 80 μg to about 120 μg biotin, about 12 mg to about 18 mg pantothenic acid, about 40 μg to about 60 μg cobalamin, about 40 mg to about 60 mg magnesium, about 1.2 mg to about 1.8 mg manganese, about 20 mg to about 30 mg zinc, about 80 μg to about 120 μg selenium, about 40 μg to about 60 μg chromium, about 1.2 mg to about 1.8 mg copper, about 12 mg to about 18 mg alpha lipoic acid, and about 4 mg to about 6 mg lutein; wherein said composition is free of added iron.

7. The method of claim **6**, wherein said composition comprises about 3000 IU carotenoids, about 100 IU vitamin E, about 400 IU vitamin D, about 300 mg vitamin C, about 20 mg thiamine, about 5 mg riboflavin, about 25 mg niacin, about 1.0 mg folic acid, about 25 mg pyridoxine, about 100 μg biotin, about 15 mg pantothenic acid, about 50 μg cyanocobalamin, about 50 mg magnesium, about 1.5 mg manganese, about 25 mg zinc, about 100 μg selenium, about 50 μg chromium, about 1.5 mg copper, about 15 mg alpha lipoic acid, and about 5 mg lutein.

8. The method of claim **6**, wherein said composition is administered to said patient daily.

9. The method of claim **6**, wherein said composition is administered to said patient orally.

10. The method of claim **6**, wherein said composition further comprises a pharmaceutically acceptable carrier.

11. The composition of claim **1**, wherein said nutritional deficiencies are a result of dietary restrictions.

12. The composition of claim **1**, wherein said nutritional deficiencies are a result of a disease state.

13. The composition of claim **12**, wherein said disease state is selected from one or more of the group consisting of anorexia, malnutrition, gastrointestinal disorders, chronic alcoholism, chronic infections, acute infections, congestive heart failure, hyperthyroidism, diabetes, cheilosis, gingivitis, hemochromatosis, hemosiderosis, and stomatitis.

14. The composition of claim **12**, wherein said disease state leads to increased oxidative stress in said patient.

15. The composition of claim **12**, wherein said disease state leads to elevated homocysteine levels in said patient.

16. The method of claim **6**, wherein said nutritional deficiencies are a result of dietary restrictions.

17. The method of claim **6**, wherein said nutritional deficiencies are a result of a disease state.

18. The method of claim **17**, wherein said disease state selected from one or more of the group consisting of anorexia, malnutrition, gastrointestinal disorders, chronic alcoholism, chronic infections, acute infections, congestive heart failure, hyperthyroidism, diabetes, cheilosis, gingivitis, hemochromatosis, hemosiderosis and stomatitis.

19. The method of claim **17**, wherein said disease state leads to increased oxidative stress in said patient.

20. The method of claim **17**, wherein said disease state leads to elevated homocysteine levels in said patient.

21. The composition of claim **1**, wherein said carotenoid comprise at least one carotenoid selected from the group consisting of alpha-carotene, beta carotene, cryptoxanthin, lutein, and zeaxanthin.

22. The composition of claim **21**, wherein said carotenoid is present in the amount of about 3000 IU.

23. The composition of claim **1**, wherein said vitamin E comprises d-alpha tocopheryl succinate.

24. The composition of claim **23**, wherein said vitamin E is present in the amount of about 100 IU.

25. The composition of claim **1**, wherein said vitamin D comprises vitamin D_3.

26. The composition of claim **25**, wherein said vitamin is present in the amount of about 400 IU.

27. The composition of claim **1**, wherein said vitamin C is in the amount of about 300 mg.

28. The composition of claim **1**, wherein said thiamine comprises thiamine HCl.

29. The composition of claim **28**, wherein said thiamine is present in the amount of about 20 mg.

30. The composition of claim **1**, wherein said riboflavin is present in the amount of about 5 mg.

31. The composition of claim **1**, wherein said niacin comprises niacinamide.

32. The composition of claim **31**, wherein said niacin is present in the amount of about 25 mg.

33. The composition of claim **1**, wherein said folic acid is present in the amount of about 1 mg.

34. The composition of claim **1**, wherein said pyridoxine comprises pyridoxine HCl.

35. The composition of claim **34**, wherein said pyridoxine is present in the amount of about 25 mg.

36. The composition of claim **1**, wherein said biotin is present in the amount of about 100 μg.

37. The composition of claim **1**, wherein said pantothenic acid comprises calcium pantothenate.

38. The composition of claim **37**, wherein said pantothenic acid is present in the amount of about 15 mg.

39. The composition of claim **1**, wherein said cobalamin comprises cyanocobalamin.

40. The composition of claim **39**, wherein said cobalamin is present in the amount of about 50 μg.

41. The composition of claim **1**, wherein said magnesium comprises magnesium oxide.

42. The composition of claim **41**, wherein said magnesium is present in the amount of about 50 mg.

43. The composition of claim **1**, wherein said manganese comprises manganese sulfate.

44. The composition of claim **43**, wherein said manganese is present in the amount of about 1.5 mg.

45. The composition of claim **1**, wherein said zinc comprises zinc oxide.

46. The composition of claim **45**, wherein said zinc is present in the amount of about 25 mg.

47. The composition of claim **1**, wherein said selenium comprises sodium selenate.

48. The composition of claim **47**, wherein said selenium is present in the amount of about 100 μg.

49. The composition of claim **1**, wherein said chromium comprises chromium chloride.

50. The composition of claim **49**, wherein said chromium is present in the amount of about 50 μg.

51. The composition of claim **1**, wherein said copper comprises cupric sulfate.

52. The composition of claim **51**, wherein said copper is present in the amount of about 1.5 mg.

53. The composition of claim **1**, wherein said alpha lipoic acid is present in the amount of about 15 mg.

54. The composition of claim **1**, wherein said lutein is present in the amount of about 5 mg.

55. The method of claim **6**, wherein said carotenoids comprise at least one carotenoid selected from the group consisting of alpha-carotene, beta-carotene, cryptoxanthin, lutein, and zeaxanthin.

56. The method of claim **55**, wherein said carotenoid is present in the amount of about 3000 IU.

57. The method of claim **6**, wherein said vitamin E comprises d-alpha tocopheryl succinate.

58. The method of claim **57**, wherein said vitamin E is present in the amount of about 100 IU.

59. The method of claim **6**, wherein said vitamin D comprises D_3.

60. The method of claim **59**, wherein said vitamin D is present in the amount of about 400 IU.

61. The method of claim **6**, wherein said vitamin C is present in the amount of about 300 mg.

62. The method of claim **6**, wherein said thiamine comprises thiamine HCl.

63. The method of claim **62**, wherein said thiamine is present in the amount of about 20 mg.

64. The method of claim **6**, wherein said riboflavin is in the amount of about 5 mg.

65. The method of claim **6**, wherein said niacin comprises niacinamide.

66. The method of claim **65**, wherein said niacin is present in the amount of about 25 mg.

67. The method of claim **6**, wherein said folic acid is present in the amount of about 1 mg.

68. The method of claim **6**, wherein said pyridoxine comprises pyridoxine HCl.

69. The method of claim **68**, wherein said pyridoxine is present in the amount of about 25 mg.

70. The method of claim **6**, wherein said biotin is present in the amount of about 100 μg.

71. The method of claim **6**, wherein said pantothenic acid comprises calcium pantothenate.

72. The method of claim **71**, wherein said pantothenic acid is present in the amount of about 15 mg.

73. The method of claim **6**, wherein said cobalamin comprises cyanocobalamin.

74. The method of claim **73**, wherein said cobalamin is present in the amount of about 50 μg.

75. The method of claim **6**, wherein said magnesium comprises magnesium oxide.

76. The method of claim **75**, wherein said magnesium is present in the amount of about 50 mg.

77. The method of claim **6**, wherein said manganese comprises manganese sulfate.

78. The method of claim **77**, wherein said manganese is present in the amount of about 1.5 mg.

79. The method of claim **6**, wherein said zinc comprises zinc oxide.

80. The method of claim **79**, wherein said zinc is present in the amount of about 25 mg.

81. The method of claim **6**, wherein said selenium comprises sodium selenate.

82. The method of claim **81**, wherein said selenium is present in the amount of about 100 μg.

83. The method of claim **6**, wherein said chromium comprises chromium chloride.

84. The method of claim **83**, wherein said chromium is present in the amount of about 50 μg.

* * * * *

Exhibit C

U.S. Patent No. 6,863,904

US006863904B2

(12) **United States Patent**
Giordano et al.

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(45) **Date of Patent: Mar. 8, 2005**

(54) **COMPOSITIONS AND METHODS FOR PROPHYLACTIC AND THERAPEUTIC SUPPLEMENTATION OF NUTRITION IN SUBJECTS**

(75) Inventors: **John A. Giordano**, West Orange, NJ (US); **Charles Balzer**, Lavalette, NJ (US)

(73) Assignee: **Everett Laboratories, Inc.**, West Orange, NJ (US)

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(58) **Field of Search** 424/630–635, 424/637–641, 643, 655, 682–683, 686, 688–689, 692, 697, 702; 514/52, 167, 168, 249, 251, 276, 345, 355, 356, 387, 440, 458, 474, 494, 499, 500, 505, 563, 706, 725, 729, 763, 824, 837, 838, 866, 893, 894, 902, 904, 905, 909, 910, 911, 925

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Primary Examiner—John Pak
(74) *Attorney, Agent, or Firm*—Preston Gates Ellis & Rouvelas Meeds LLP

(57) **ABSTRACT**

The present invention relates to compositions without added iron and methods for prophylactic nutritional supplementation and therapeutic nutritional supplementation. Specifically, the method involves administering to an individual a composition comprising carotenoids, vitamin E, vitamin D, vitamin C, thiamine, riboflavin, niacin, folic acid, pyridoxine, biotin, pantothenic acid, cobalamin, magnesium, manganese, zinc, selenium, chromium, copper, alpha lipoic acid, and lutein, wherein the composition is free of added iron.

110 Claims, No Drawings

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COMPOSITIONS AND METHODS FOR PROPHYLACTIC AND THERAPEUTIC SUPPLEMENTATION OF NUTRITION IN SUBJECTS

CROSS REFERENCE TO RELATED APPLICATION

The present application is a continuation of and claims, under 35 USC §120, the benefit of U.S. patent application Ser. No. 09/982,205, filed on Oct. 19, 2001, which is now U.S. Pat. No. 6,660,293, and claims, under 35 USC §119, the benefit of priority of U.S. provisional patent application Ser. No. 60/301,443, filed Jun. 29, 2001, which are expressly incorporated fully herein by reference.

FIELD OF THE INVENTION

The present invention relates to compositions comprising various vitamins and minerals, and without added iron, and methods for using these compositions for prophylactic nutritional supplementation and therapeutic nutritional supplementation in, for example, physiologically stressful conditions and to minimize the effect of exogenous iron supplementation.

BACKGROUND OF THE INVENTION

Nutrition plays a critical role in maintaining good health. Proper nutrition prevents dietary deficiencies, and also protects against the development of disease. Proper nutrition plays an increasingly important role as the body faces physiological stress. For example, as the body ages it suffers significant physiological stresses. Specifically, as the body metabolism shifts to accumulating larger fat stores and decreasing lean body mass, this increase in body weight may lead to obesity and associated conditions such as diabetes, cardiovascular disease, hypertension, osteoarthritis, and cancer. Other conditions, such as anorexia, malnutrition, gastrointestinal disorders, chronic alcoholism, chronic infections, acute infections, congestive heart failure, hyperthyroidism, poorly controlled diabetes, cheilosis, gingivitis, stomatitis and dietary restrictions, often result in physiological stresses that may be exacerbated by poor nutrition. In particular, these disease states may result in increased oxidative stress or elevated homocysteine levels that further compromise health.

Thus, nutritional supplementation serves a vital role in protecting against poor nutrition and disease. More specifically, nutritional supplementation may provide the necessary vitamins, minerals, and other nutrients that might otherwise be lacking in the diet, and provide the nutritional defense against disease development. The invention herein provides for compositions and methods, specifically using an iron-free multi-vitamin/mineral/antioxidant formulation, designed to optimize health and wellness, minimize oxidative stress, and normalize homocysteine levels.

SUMMARY OF THE INVENTION

The present invention provides nutritional compositions without iron and methods of using these compositions for both prophylactic and therapeutic nutritional supplementation, specifically in physiologically stressful conditions. Specifically, the present invention relates to novel compositions of vitamins and minerals, without exogenous iron, that can be used to supplement the nutritional deficiencies observed in patients with anorexia, malnutrition, gastrointestinal disorders, chronic alcoholism, chronic infections, acute infections, congestive heart failure, hyperthyroidism, poorly controlled diabetes, cheilosis, gingivitis, stomatitis, and/or dietary restrictions. In addition, the compositions may be used to treat the nutritional deficiencies of patients suffering from a disease state that results in increased oxidative stress or elevated homocysteine levels.

The compositions of the present invention include various vitamins and minerals that improve the nutritional state of a patient; these compositions preferably may be used therapeutically or prophylacticly. The vitamins of the present invention may preferably comprise one or more of carotenoids, vitamin E, vitamin D_3, vitamin C, thiamine, riboflavin, niacin, folic acid, pyridoxine, biotin, pantothenic acid, and cyanocobalamin. The minerals of the present invention may preferably include one or more of magnesium, manganese, zinc, selenium, chromium, and copper. In addition, the present invention may preferably comprise other nutritional elements, such as alpha lipoic acid, and/or lutein. The compositions of the present invention preferably do not include exogenous iron as an added component.

In a preferred embodiment, the compositions of the present invention comprise carotenoids in a range of about 2400 IU to about 3600 IU, vitamin E in a range of about 80 IU to 120 IU, vitamin D in a range of about 320 IU to about 480 IU, vitamin C in a range of about 240 mg to 360 mg, thiamine in a range of about 16 mg to 24 mg, riboflavin in a range of about 4 mg to about 6 mg, niacin in a range of about 20 mg to about 30 mg, folic acid in a range of about 0.8 mg to 1 mg, pyridoxine provided in a range of about 20 mg to 30 mg, biotin in a range of about 80 μg to about 120 μg, pantothenic acid in a range of about 12 mg to about 18 mg, cobalamin in a range of about 40 μg to about 60 μg, magnesium in a range of about 40 mg to about 60 mg, manganese in a range of about 1.2 mg to about 1.8 mg, zinc in a range of about 20 mg to about 30 mg, selenium in a range of about 80 μg to 120 μg, chromium in a range of about 40 μg to about 60 μg, copper in a range of about 1.2 mg to about 1.8 mg copper, lipoic acid in a range of about 12 mg to about 18 mg, and lutein in a range from about 4 mg to 6 mg, wherein these compositions are free of added iron.

In another embodiment of the compositions of the present invention, vitamin E is present as d-alpha tocopheryl succinate, vitamin D is vitamin D_3, niacin is niacinamide, chromium is chromium chloride, selenium is present as sodium selenate, zinc is zinc oxide, carotenoids consist of alpha-carotene, beta-carotene, cryptoxanthin, lutein and zeaxanthin, magnesium is magnesium oxide, manganese is present as manganese sulfate, and copper is cupric sulfate.

In a further preferred embodiment of the present invention, the composition includes about 3000 IU carotenoids, about 100 IU d-alpha tocopheryl succinate, about 400 IU vitamin D_3, about 300 mg vitamin C, about 20 mg thiamine, about 5 mg riboflavin, about 25 mg niacinamide, about 1.0 mg folic acid, about 25 mg pyridoxine HCl, about 100 μg biotin, about 15 mg calcium pantothenate, about 50 μg cyanocobalamin, about 50 mg magnesium oxide, about 1.5 mg manganese sulfate, about 25 mg zinc oxide, about 100 μg selenium, about 50 μg chromium chloride, about 1.5 mg cupric sulfate, about 15 mg alpha lipoic acid, and about 5 mg lutein, wherein this composition is free of added iron.

In addition, the compositions of the present invention may be administered to an individual on a daily basis and the composition may be administered orally. Furthermore, the

compositions of the present invention may include a pharmaceutically acceptable carrier.

The present invention also relates to methods for supplementing nutritional deficiencies in a patient or person by administering a composition comprising carotenoids, vitamin E, vitamin D, vitamin C, thiamine, riboflavin, niacin, folic acid, pyridoxine, biotin, pantothenic acid, cobalamin, magnesium, manganese, zinc, selenium, chromium, copper, alpha lipoic acid, and lutein, wherein this composition is free of added iron.

The methods of the present invention may be used to treat patients suffering from anorexia, malnutrition, gastrointestinal disorders, chronic alcoholism, chronic infections, acute infections, congestive heart failure, hyperthyroidism, poorly controlled diabetes, cheilosis, gingivitis, stomatitis, and dietary restrictions. In addition, these methods may be used to treat the nutritional deficiencies in patients suffering from a disease state that results in increased oxidative stress or elevated homocysteine levels.

In a preferred embodiment, the methods of the present invention utilize compositions comprising carotenoids in a range of about 2400 IU to about 3600 IU, vitamin E in a range of about 80 IU to about 120 IU, vitamin D in a range of about 320 IU to about 480 IU, vitamin C in a range of about 240 mg to 360 mg, thiamine in a range of about 16 mg to about 24 mg, riboflavin in a range of about 4 mg to about 6 mg, niacin in a range of about 20 mg to about 30 mg, folic acid in a range of about 0.8 mg to about 1 mg, pyridoxine provided in a range of about 20 mg to about 30 mg, biotin in a range of about 80 μg to about 120 μg, pantothenic acid in a range of about 12 mg to about 18 mg, cobalamin in a range of about 40 μg to about 60 μg, magnesium in a range of about 40 mg to about 60 mg, manganese in a range of about 1.2 mg to about 1.8 mg, zinc in a range of about 20 mg to about 30 mg, selenium in a range of about 80 μg to about 120 μg, chromium in a range of about 40 μg to about 60 μg, copper in a range of about 1.2 mg to about 1.8 mg copper, lipoic acid in a range of about 12 mg to about 18 mg, and lutein in a range from about 4 mg to about 6 mg, wherein these compositions are free of added iron.

In a further preferred embodiment, the methods of the present invention utilize a composition comprising about 3000 IU carotenoids, about 100 IU d-alpha tocopheryl succinate, about 400 IU vitamin D_3, about 300 mg vitamin C, about 20 mg thiamine, about 5 mg riboflavin, about 25 mg niacinamide, about 1.0 mg folic acid, about 25 mg pyridoxine HCl, about 100 μg biotin, about 15 mg calcium pantothenate, about 50 μg cyanocobalamin, about 50 mg magnesium oxide, about 1.5 mg manganese sulfate, about 25 mg zinc oxide, about 100 μg selenium, about 50 μg chromium chloride, about 1.5 mg cupric sulfate, about 15 mg alpha lipoic acid, and about 5 mg lutein, wherein this composition is free of added iron.

DETAILED DESCRIPTION

Proper nutrition is essential for maintaining health and preventing diseases. The compositions and methods of the present invention provide the means to optimize good health by utilizing vitamin, mineral, and antioxidant nutritional supplementation. More specifically, the compositions of the present invention contain a variety of antioxidants, which may minimize free radical concentrations and minimize the deleterious effects of oxidative stress, and vitamins and minerals that support normal levels of homocysteine. It is to be understood that the terminology used herein is used for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention. It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise.

The compositions of the present invention may preferably comprise antioxidant factors that may protect against oxidative stress. Oxidative stress occurs as the body's natural use of oxygen creates unstable molecules known as free radicals, which steal stable electron partners from other molecules, launching more free radicals and increased molecular and cellular instability. This 'oxidative stress' is implicated in over 200 diseases, including cardiovascular disease and cancer, which are attributed to free radical oxidation. Rock et al., 96 J. Am. Dietary Assoc. 693–702 (1996). For example, lipid peroxidation is the initiating step in the oxidation of low-density lipoproteins (LDL). In turn, the lipid peroxides oxidate other lipoproteins, which are taken up by the cells of the arterial wall. Eventually, the deposited oxidized lipoproteins form an atherosclerotic plaque. Id. The antioxidant components of the compositions and methods described herein may preferably include one or more of vitamin E, selenium, vitamin C, carotenoids, lutein, and lipoic acid.

The compositions and methods of the present invention also may preferably include B-complex vitamins, which are critical for health as each is part of one or more coenzymes in metabolizing food properly. This class of vitamins is water-soluble nutrients, not stored significantly in the body. Importantly, the B-complex vitamins may help normalize homocysteine levels and metabolism. High homocysteine levels have been correlated directly with increased risk of atherosclerosis and other heart disease. Although the exact mechanism by which homocysteine contributes to heart disease is not fully understood, it may act as an endothelial irritant that promotes atherosclerosis by inducing endothelial dysfunction. B-complex vitamins are required for the proper function of the homocysteine metabolic pathway, thus maintaining adequate levels of these vitamins may assist in normalizing homocysteine levels and maintaining good health. The B-complex vitamins of the present compositions and methods may preferably include one or more of thiamin (B_1), riboflavin (B_2), niacin (B_3), pantothenic acid, biotin, folic acid, pyridoxine (B_6) and cobalamin (B_{12}).

Minerals are inorganic, or non-carbon-containing, elements that are critical for healthy physiological processes, and are contemplated in the compositions and methods of the present invention. For example, minerals act as cofactors for hundreds of enzymes that range from those associated, for example, with food digestion, nucleic acid production, protein synthesis to antioxidant enzymes. One particular mineral, chromium, is essential in healthy insulin function, as it plays a direct role in insulin's interactions at the cellular level. The minerals of the compositions and methods of the present invention may preferably include one or more of chromium, zinc, copper, magnesium, and manganese.

Another mineral, iron, is specifically excluded from the compositions and methods of the present invention. Although iron is an essential mineral with many functions, iron has also been implicated as a catalyst for lipid oxidation. Specifically, lipid oxidation associated with LDL cholesterol has been correlated strongly with an increased risk of cardiovascular disease. Moreover, some older patients exhibit sensitivity to iron or build-up of iron concentration in the liver. Although iron supplementation may be indicated in specific population groups or disease states, universal supplementation may not always be recommended. Hence, the compositions and methods of the present invention are preferably free of added iron.

Vitamin D may preferably be a component of the compositions and methods of the present invention. Vitamin D is a fat-soluble "hormone like" substance essential for healthy bones. This vitamin increases the absorption of calcium and phosphorous from the gastrointestinal tract, and improves essential mineral resorption into bone tissue. Vitamin D can be converted to its active form from exposure of the skin to sunlight. This fact is among the reasons why vitamin D deficiency is common in the elderly, notably the institutionalized, who spend little or no time out of doors. Deficiencies lead to increased bone turnover and loss, and when severe, osteomalacia or softening of the bones. Supplementation with vitamin D has been shown to moderately reduce bone loss, increase serum 25-hydroxyvitamin D, and decrease serum parathyroid hormone levels. Dawson-Hughes et al., 337 New Eng. J. Med. 670–76 (1997); Lips et al., 86 J. Clin. Endocrinol. METAB. 1212–21 (2001).

Preferably, the vitamin D of the compositions and methods of the present invention is vitamin D_3. In the body, vitamin D_3 is produced when its precursor is exposed to ultraviolet irradiation (e.g., sunlight) and then hydroxylated in the liver to form 25-hydroxyvitamin D_3, the major form of vitamin D in the circulation. This form of the vitamin may be hydroxylated again in the kidney, yielding 1,25-hydroxyvitamin D_3, the most potent form of vitamin D. As noted above, vitamin D_3 plays a role in the maintenance of calcium and phosphorus homeostasis, but it is also active in cell differentiation and immune function. In a preferred embodiment of the invention, vitamin D_3 is present in the amount ranging from about 320 IU to about 480 IU. In a particularly preferred embodiment, vitamin D_3 is present in an amount of about 400 IU.

As discussed previously, the antioxidant components of the compositions and methods described herein preferably include vitamin E, selenium, vitamin C, carotenoids. lutein, and lipoic acid.

Vitamin E is a fat-soluble vitamin antioxidant found in biological membranes where it protects the phospholipid membrane from oxidative stress. More specifically, alpha-tocopherol, the most abundant and most active form of the vitamin E family, is the principle lipid-soluble, chain breaking antioxidant in tissue and plasma. Recommended Dietary Allowances 99–101 (Nat'l Research Council, 10th ed., 1989) (hereinafter "RDA"). Vitamin E inhibits the oxidation of unsaturated fatty acids by trapping peroxyl free radicals. It is also an antiatherogenic agent, and studies have demonstrated a reduced risk of coronary heart disease with increased intake of vitamin E. Stampfer et al., 328 New Eng. J. Med. 1444–49 (1993). Vitamin E is available in various forms known to those of skill in the art. In a preferred embodiment of the present invention, vitamin E is present in an amount ranging from about 80 IU to about 120 IU. In a particularly preferred embodiment of the invention, vitamin E is present d-alpha tocopheryl succinate. A preferred embodiment of the invention includes about 100 IU d-alpha tocopheryl succinate.

Along with vitamin E, the mineral selenium is a component of the antioxidant enzyme, glutathione peroxidase, which plays a critical role in the control of oxygen metabolism, particularly catalyzing the breakdown of hydrogen peroxide. Burk, 3 Ann. Rev. Nutrition 53–70 (1983). Glutathione peroxidase prevents the generation of free radicals and decreases the risk of oxidative damage to numerous tissues, including the vascular system. Holben, 99 J. Am. Dietary Assoc. 836–43 (1999). Another selenoprotein is the enzyme iodothyronine 5'-diodinase that converts thyroxine (T_4) to triiodothyronine (T_3). Selenium is available in many forms known to those of ordinary skill in the art. In a preferred embodiment of the present invention, selenium is included in a range of about 80 μg to about 120 μg. In a preferred embodiment of the invention, selenium is present as sodium selenate. A preferred embodiment of the invention includes about 100 μg sodium selenate.

Vitamin C (also known as ascorbic acid) is another antioxidant present in the invention described herein. The major biochemical role of the water-soluble vitamin C is as a co-substrate in metal catalyzed hydroxylations, and it has antioxidant properties in interacting directly with superoxide hydroxyl radicals and singlet oxygen. Vitamin C also provides antioxidant protection for folate and vitamin E, keeping vitamin E in its most potent form. It also enhances the absorption of iron. RDA, at 115. In addition, vitamin C is required for collagen synthesis, epinephrine synthesis, and bile acid formation. Moreover, vitamin C has been implicated in inhibiting atherosclerosis by being present in extracellular fluid of the arterial wall and potentiating nitric oxide activity, thus normalizing vascular function. A preferred embodiment of the compositions of the present invention includes a supplemental dose of vitamin C, preferably in the amount of about 240 mg to about 360 mg. A preferred embodiment of the present invention includes about 300 mg of vitamin C.

Along with vitamins E and C, and selenium, carotenoids are a group of antioxidants embodied in the present invention. There are over 600 carotenoids occurring naturally in fruits and vegetables. Many of these fat-soluble compounds, of which beta-carotene is a well-known example, have pro-vitamin A activity as well as antioxidant activity. Less-known carotenoids include alpha-carotene, lutein, cryptoxanthine, and zeaxanthin. The compositions and methods herein include a cartonoid complex that closely mirrors that found naturally in fruits and vegetables. In particular, the carotenoids of the present invention may preferably include alpha-carotene, beta-carotene, cryptoxanthin, lutein, and zeaxanthin. In particular, lutein and zeaxanthin are the major carotenoids that make up the macular pigment of the eye's retina, and their antioxidant properties protect the eye from light-induced damage and macular degeneration. Berendschot et al., 41 Invest. Ophthalmol. Vis. Sci. 3322–26 (2000). In a preferred embodiment of the invention, carotenoids are included in a range of about 2400 IU to about 3600 IU. In a more preferred embodiment of the invention, the carotenoids include a mixture of alpha-carotene, beta-carotene, cryptoxanthin, lutein, and zeaxanthin. A preferred embodiment of the invention includes about 3000 IU of a mixture of alpha-carotene, beta-carotene, cryptoxanthin, lutein, and zeaxanthin.

Lutein is also preferably included in the compositions and methods described herein and is preferably included in an amount distinguished from that included in the mixed carotenoids. Regarding the antioxidant activity of lutein, scientists have demonstrated that lutein is an effective antioxidant capable of scavenging peroxyl radicals and quenching reactive oxygen species. Rapp et al., 41 Invest. Ophthalmol. Vis. Sci. 1200–09 (2000). Thus, the compositions and methods of the present invention may include lutein, preferably in the amount ranging from about 4 mg to about 6 mg. A preferred embodiment of the invention comprise about 5 mg lutein.

Lipoic acid is an antioxidant and is preferably included in the compositions and methods of the present invention.

Known as the "universal antioxidant," alpha lipoic acid is both a lipid- and water-soluble antioxidant that works synergistically with other antioxidants in the cell's mitochondria. In addition to working with other antioxidant nutrients, lipoic acid has powerful, pro-antioxidant enzyme properties. Alpha lipoic acid is also a cofactor for several regulatory enzymes, including pyruvate dehydrogenase, and appears to have an effect on glucose transport and utilization. Rudich et al., 42 DIABETOLOGIA 949–57 (1999). Alpha lipoic acid also increases tocopherol activity and acts as a metal chelator. Furthermore, alpha lipoic acid improves microvascular perfusion. Haak et al., 108 EXPERIMENTAL & CLINICAL ENDOCRINOLOGY & DIABETES 168–74 (2000). A preferred embodiment of the compositions of the present invention comprises alpha lipoic acid in the amount ranging from about 12 mg to about 18 mg. A particularly preferred embodiment of the present invention comprises about 15 mg of lipoic acid.

In addition to antioxidants, the compositions and methods of the present invention also preferably include one or more B-complex vitamins such as thiamin (B_1), riboflavin (B_2), niacin (B_3), pantothenic acid (B_5), biotin, folic acid, pyridoxine (B_6) and cobalamin (B_{12}).

Thiamine (vitamin B_1) plays a role in carbohydrate metabolism and neural function. It is a coenzyme for the oxidative decarboxylation of alpha-ketoacids (e.g., alpha-ketoglutarate and pyruvate) and for transketolase which is a component of the pentose phosphate pathway. Folate deficiency and malnutrition inhibit the activity of thiamine. RDA, at 123. One embodiment of the compositions of the present invention may comprise thiamine, preferably in the amount ranging from about 16 mg to about 24 mg. In a preferred embodiment of the present invention, the form of thiamine is thiamine HCl. A preferred embodiment of the invention comprises about 20 mg thiamine HCl.

Riboflavin (vitamin B_2) is a component of two flavin coenzymes, flavin mononucleotide (FMN) and flavin adenine dinucleotide (FAD). These flavoenzymes are involved in a number of oxidation-reduction reactions including the conversion of pyridoxine and niacin. RDA, at 132. Flavoenzymes also play a role in a number of metabolic pathways such as citric acid cycle, amino acid deamination, purine degradation, and fatty acid oxidation and thus help to maintain carbohydrate, amino acid, and lipid metabolism. In one embodiment, the compositions and methods of the present invention comprise riboflavin, preferably in the amount ranging from about 4 mg to about 6 mg. A preferred embodiment of the invention comprises about 5 mg of riboflavin.

Niacin, also called vitamin B_3, is the common name for two compounds: nicotinic acid (also called niacin) and niacinamide (also called nicotinamide). Niacin and is particularly important for maintaining healthy levels and types of fatty acids. Niacin is also required for the synthesis of pyroxidine, riboflavin, and folic acid. RDA, at 137. Administration of niacin may also produce a reduction in total cholesterol, LDL, and very low density lipoprotein (VLDL) levels; and an increase in high density lipoprotein (HDL) cholesterol levels. Nicotinamide adenine dinucleotide (NAD) and NAD phosphate (NADP) are active coenzymes of niacin. These coenzymes are involved in numerous enzymatic reactions such as glycolysis, fatty acid metabolism, and steroid synthesis. Henkin et al., 91 AM. J. MED. 239–46 (1991). One embodiment of the compositions and methods of the present invention may comprise niacin, preferably in the amount ranging from about 20 mg to about 30 mg. In a preferred embodiment of the invention, niacin is present in the form of niacinamide. A preferred embodiment of the invention comprises about 25 mg of niacinamide.

Folic acid (vitamin B_8), also called folate or methylfolate, is essential for the formation of red and white blood cells within bone marrow and also plays a role in heme formation. RDA, at 150. Folic acid in its active form, tetrahydrofolate, is a coenzyme that is involved in the transfer of methyl groups and it plays a role in DNA synthesis, purine synthesis, and amino acid synthesis, such as the conversion of glycine to serine and the transformation of homocysteine to methionine. The activation of folic acid requires a vitamin B_{12}-dependent transmethylation and vitamin B_{12} is also necessary for folic acid delivery to tissues. Id. One embodiment of the compositions and methods of the present invention may comprise folic acid, preferably in the amount ranging from about 0.8 mg to about 1.0 mg. A preferred embodiment of the invention comprises about 1 mg of folic acid.

Pyridoxine (vitamin B_6) is another B-complex vitamin included in the compositions and methods described herein. The administration of pyridoxine may reduce the levels of homocysteine. Bostom et al., 49 KIDNEY INT. 147–52 (1996). The active forms of pyridoxine, pyridoxal-5'-phosphate (PLP) and pyridoxamine-5'-phosphate, are coenzymes for numerous enzymes and as such, are essential for gluconeogenesis, niacin formation, and erythrocyte metabolism. RDA, at 142–143. Pyridoxine is a coenzyme for both cystathionine synthase and cystathionase, enzymes that catalyze the formation of cysteine from methionine. Homocysteine is an intermediate in this process and elevated levels of plasma homocysteine are recognized as a risk factor for vascular disease. Robinson et al., 94 CIRCULATION 2743–48 (1996). Hence, one embodiment of the compositions and methods of the present invention may comprise pyridoxine, preferably in the amount ranging from about 20 mg to about 30 mg. In a preferred embodiment of the invention, pyridoxine is in the form of pyridoxine HCl. A preferred embodiment of the invention comprises about 25 mg pyridoxine HCl.

Biotin, another water-soluble B-complex vitamin, acts a coenzyme for a number of carboxylases, and thus has an important role in gluconeogenesis, fatty acid metabolism, and amino acid metabolism. RDA, at 166. For example, biotin serves as a carboxyl carrier for pyruvate carboxylase, which is involved in gluconeogenesis; acetyl CoA carboxylase, which is involved in fatty acid synthesis; and propionyl-CoA carboxylase, which is involved in glucose production. Researchers believe that biotin inhibits the effects of uremic toxins on tubulin polymerizaton. Braguer et al., 57 NEPHRON 192–96 (1991). Thus, one embodiment of the compositions and methods of the present invention comprises biotin, preferably in the amount ranging from about 80 μg to about 120 μg. A preferred embodiment of the invention comprises about 100 μg biotin.

Pantothenic acid (vitamin B_5) is a component of both the coenzyme A macromolecule and the acyl-carrier protein. These coenzymes function as carriers for acyl groups and are required for the synthesis of fatty acids, cholesterol, steroid hormones, and neurotransmitters. The coenzyme A complex also has a major role in the acetylation and acylation of numerous proteins. RDA, at 169. One embodiment of the compositions and methods of the present invention comprises pantothenic acid, preferably in the amount ranging from about 12 mg to about 18 mg. In a preferred embodiment of the invention, pantothenic acid is present as calcium pantothenate. A preferred embodiment of the invention comprises about 15 mg calcium pantothenate.

Cobalamin (vitamin B_{12}), another important vitamin included in the compositions and methods described herein, can be converted to the active coenzymes, methylcobalamin and 5'-deoxyadenosylcobalamin. These coenzymes are necessary for folic acid metabolism, conversion of coenzyme A, and myelin synthesis. For example, methylcobalamin catalyzes the demethylation of a folate cofactor, which is involved in DNA synthesis. A lack of demethylation may result in folic acid deficiency. RDA, at 159–160. Deoxyadenosylcobalamin is the coenzyme for the conversion of methylmalonyl-CoA to succinyl-CoA, which plays a role in the citric acid cycle. Importantly, cobalamin, along with pyridoxine and folic acid in implicated in the proper metabolism of homocysteine. Cobalamin is available as cyanocobalamin, methylcobalamin, hydroxocobalamin, adenosylcobalamin, and hydroxycyanocobalamin. One embodiment of the compositions and methods of the present invention may comprise cobalamin, preferably in the amount ranging from about 40 μg to about 60 μg. In a preferred embodiment of the invention, cobalamin is present as cyanocobalamin. A preferred embodiment of the invention includes about 50 μg cyanocobalamin.

As noted previously, minerals are inorganic elements that play a crucial role in physiological processes in the body relating to good health. The compositions and methods of the present invention may comprise minerals, and, in a preferred embodiment, comprise one or more of selenium, discussed above, and magnesium, manganese, zinc, chromium, and copper.

Magnesium is found primarily in both bone and muscle. Magnesium is an essential component for over 300 enzymes, including enzymes of biosynthetic pathways, glycolysis, protein synthesis, transketolase reactions, and membrane transport. Magnesium is also involved in the formation of cAMP, a cytosolic second messenger that plays a role in cell signaling mechanisms. In addition, magnesium functions both synergistically and antagonistically with calcium in neuromuscular transmission. RDA, at 188. Specifically, magnesium is critical for the maintenance of electrochemical potentials of nerve and muscle membranes and the neuromuscular junction transmissions, particularly important in the heart. Not surprisingly, magnesium deficiency is tied to cardiovascular disease and hypertension. Agus et al., 17 Crit. Care Clinics 175–87 (2001). Indeed, oral magnesium therapy improves endothelial function in patients with coronary disease. Shechter et al., 102 Circulation 2353–58 (2000). Yet, most individuals in the U.S. receive only about seventy-five percent of the magnesium they need from their diets. Magnesium is available in a variety of salts. One embodiment of the compositions and methods of the present invention comprises magnesium, preferably in the amount ranging from about 40 mg to about 60 mg. In a preferred embodiment of the invention, magnesium is present as magnesium oxide. A preferred embodiment of the invention comprises about 50 mg magnesium oxide.

Manganese, like magnesium, plays a key role in multiple enzymes and is needed for healthy skin, bone, and cartilage formation, as well as glucose tolerance. For example, manganese is a cofactor for enzymes such as glutamine synthetase, pyruvate carboxylase, and mitochrondrial superoxide dismutase. RDA, at 230. In particular, manganese is essential for glycoprotein and proteoglycan synthesis, and thus is involved in the formation of connective and skeletal tissue, as well as carbohydrate and lipid metabolism. It also helps activate superoxide dismutase, an important antioxidant enzyme. Manganese is available in many forms known to those of ordinary skill in the art, including manganese sulfate, manganese oxide, manganese oxy-sulfate, and manganese proteinate. One embodiment of the compositions and methods of the present invention comprises manganese, preferably in the amount ranging from about 1.2 mg to about 1.8 mg. In a preferred embodiment, manganese is present as manganese sulfate. A preferred embodiment of the invention comprises about 1.5 mg of manganese sulfate.

Zinc plays a role in numerous metabolic activities such as nucleic acid production, protein synthesis, and development of the immune system. There are more than 200 zinc metalloenzymes including aldolase, alcohol dehydrogenase, RNA polymerase, and protein kinase C. Zima et al., 17 Blood Purif. 182–86 (1999). Moreover, zinc stabilizes RNA and DNA structures, forms zinc fingers in nuclear receptors, and is a component of chromatin proteins involved in transcription and replication. Zinc is available in many forms, such as zinc oxide and zinc sulfate. One embodiment of the compositions and methods of the present invention comprises zinc, preferably in the amount ranging from about 20 mg to about 30 mg. More preferably, zinc may be present as zinc oxide. A preferred embodiment of the invention comprises about 25 mg zinc oxide.

The trace mineral chromium harmonizes with insulin at the cellular level to optimize the release of energy from glucose, as well as maintaining proper cellular lipid or fat metabolism. Specifically, chromium increases insulin binding to cells, insulin receptor number, and activates the insulin receptor kinase leading to increased insulin sensitivity. Several studies suggest that adequate chromium levels are needed for optimal glycemic control. See, e.g., Anderson et al., 26 Diabetes Metabolabolism 22–27 (2000); Vincent, 130 J. Nutrition 715–18 (2000). The concentration of chromium declines with age, and coronary artery disease appears to be associated with low levels of chromium. RDA, at 241. Yet, ninety percent of adults in the U.S. consume less than the recommended minimum amount of chromium. Chromium is available in various forms known to those skilled in the art, such as chromium chloride, chromium sulfate, chromium potassium sulfate, and chromium picolinate. One embodiment of the compositions and methods of the present invention comprises chromium, preferably in the amount ranging from about 40 μg to about 60 μg. Preferably, chromium is supplied as chromium chloride. A preferred embodiment of the invention comprises 50 μg chromium chloride.

Copper is a component of several enzymes associated with numerous physiological functions, including, for example, oxidase enzymes, such as cytochrome c oxidase, and cytosolic superoxide dismutase. RDA, at 224. In particular, copper is a cofactor of lysyl oxidase, which is critical for lysine cross-linking in collagen and elastin. Copper acts as an antioxidant, and promotes the synthesis of melanin and catecholamines. In addition, copper is present in the blood as ceruloplasmin which is involved in oxidizing iron prior to transport to the plasma. Copper is available in multiple forms, such as cupric oxide, copper sulfate, cupric acetate, and alkaline copper carbonate. One embodiment of the compositions and methods of the present invention comprises copper, preferably in the amount ranging from about 1.2 mg to about 1.8 mg. In a preferred embodiment of the invention, copper comprises cupric sulfate. A preferred embodiment comprises about 1.5 mg cupric sulfate.

The compositions and methods of the present invention represent a combination of essential vitamins and minerals that work together with various metabolic systems and physiological responses of the human body. The active

ingredients are available from numerous commercial sources, and in several active forms or salts thereof, known to those of ordinary skill in the art. Hence, the compositions and methods of the present invention are not limited to any particular form of the vitamin or mineral ingredient described herein.

The ingredients of the present invention are preferably combined into a composition which may be in the form of a solid powder, caplets, tablets, lozenges, pills, capsules, or a liquid, and which may be administered alone or in suitable combination with other components. For example, the composition of the present invention may be administered in one or more caplets or lozenges as practical for ease of administration. Each of the vitamins and minerals is commercially available, and can be blended to form a single composition or can form multiple compositions, which may be co-administered.

To prepare the compositions of the present invention, each of the active ingredients may be combined in intimate admixture with a suitable carrier according to conventional compounding techniques. The carrier may take a wide variety of forms depending upon the form of the preparation desired for administration, e.g., oral, sublingual, nasal, topical patch, or parenteral. Preferably, the composition may consists of one to three caplets or lozenges, the composition of each being identical to each other caplet or lozenge.

In preparing the composition in oral dosage form, any of the usual media may be utilized. For liquid preparations (e.g., suspensions, elixirs, and solutions), media containing, for example water, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used. Carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like may be used to prepare oral solids (e.g., powders, caplets, pills, tablets, capsules, and lozenges). Controlled release forms may also be used. Because of their ease in administration, caplets, tablets, pills, and capsules represent the most advantageous oral dosage unit form, in which case solid carriers are employed. If desired, tablets may be sugar coated or enteric coated by standard techniques. All of these pharmaceutical carriers and formulations are well known to those of ordinary skill in the art. See, e.g., WADE & WALLER, HANDBOOK OF PHARMACEUTICAL EXCIPIENTS (2nd ed. 1994).

Other objectives, features and advantages of the present invention will become apparent from the following specific examples. The specific examples, while indicating specific embodiments of the invention, are provided by way of illustration only. Accordingly, the present invention also includes those various changes and modifications within the spirit and scope of the invention that may become apparent to those skilled in the art from this detailed description. The invention will be further illustrated by the following non-limiting examples.

EXAMPLE 1

A composition of the following formulation was prepared in caplet form, including the appropriate excipients, by standard methods known to those of ordinary skill in the art:

Carotenoids (Alpha-Carotene, Beta-Carotene, Cryptoxanthin, Lutein, Zeaxanthin)	3000 IU
Vitamin E	100 IU
Vitamin D_3	400 IU
Vitamin C (Ascorbic Acid)	300 mg
Vitamin B_1 (Thiamine HCl)	20 mg
Vitamin B_2 (Riboflavin)	5 mg
Niacin (Niacinamide)	25 mg
Folic Acid	1 mg
Vitamin B_6 (Pyridoxine HCl)	25 mg
Biotin	100 μg
Pantothenic Acid (Calcium Pantothenate)	15 mg
Vitamin B_{12} (Cyanocobalamin)	50 μg
Magnesium (Magnesium Oxide)	50 mg
Manganese (Manganese Sulfate)	1.5 mg
Zinc (Zinc Oxide)	25 mg
Selenium (Sodium Selenate)	100 μg
Chromium (Chromium Chloride)	50 μg
Copper (Cupric Sulfate)	1.5 mg
Alpha Lipoic Acid	15 mg
Lutein	5 mg

EXAMPLE 2

A study is undertaken to evaluate the effectiveness of the composition of the present invention in the treatment of patients. The objective of the study is to determine whether oral intake of the composition results in an improvement of the nutritional status of the patient, either therapeutically or prophylacticly.

A double-blind, placebo controlled study is conducted over a twelve-month period. A total of sixty subjects (30 men and 30 women), aged 40 to 85 years, suffering from dietary restrictions or a disease state such as anorexia, malnutrition, gastrointestinal disorders, chronic alcoholism, chronic infections, acute infections, congestive heart failure, hyperthyroidism, poorly controlled diabetes, cheilosis, gingivitis, sensitivity to iron, hemosiderosis, hemochromatosis, or stomatitis, or a propensity or disposition to such a disease state are chosen for the study. An initial assessment of nutritional status is conducted utilizing methods such as the peroxide hemolysis test to assess vitamin E deficiency, measurement of erythrocyte transketolase activity to determine thiamine levels, determination of erythrocyte glutathione reductase activity to assess riboflavin status, and high performance liquid chromatography to directly measure PLP and pyridoxine levels.

The sixty subjects are separated into two separate groups of fifteen men and fifteen women. In the first group, each subject is administered 1 to 2 caplets, daily, of the composition as described in Example 1. In the second group (control), each subject is administered 1 to 2 placebo caplets, daily.

An assessment of nutritional status for each subject is measured at one-month intervals for a twelve month period as described above and the data is evaluated using multiple linear regression analysis and a standard students t-test. In each analysis the baseline value of the outcome variable is included in the model as a covariant. Treatment by covariant interaction effects is tested by the method outlined by Weigel & Narvaez, 12 CONTROLLED CLINICAL TRIALS 378–94 (1991). If there are no significant interaction effects, the interaction terms are removed from the model. The regression model assumptions of normality and homogeneity of variance of residuals are evaluated by inspection of the plots of residuals versus predicted values. Detection of the temporal onset of effects is done sequentially by testing for the presence of significant treatment effects at 16, 12, and 8 weeks, proceeding to the earlier time in sequence only when significant effects have been identified at each later time

period. Changes from the baseline within each group are evaluated using paired t-tests. In addition, analysis of variance is performed on all baseline measurements and measurable subject characteristics to assess homogeneity between groups. All statistical procedures are conducted using the Statistical Analysis System (SAS Institute Inc., Cary, N.C.). An alpha level of 0.05 is used in all statistical tests.

A statistically significant improvement in the nutritional status is preferably observed in the treated subjects upon completion of the study over the controls. The study may also look at the progression of the disease state, or the prevention or delay of a disease or disease state, or the reduction of the severity of a disease. The differences between nutritional state or the progression of the disease state, or the prevention or delay of a disease or disease state or the reduction of the severity of a disease, between the treated subjects and controls are preferably statistically significant and or observable by clinical or other tests or evaluations. Therefore, the study confirms that oral administration of the composition of the present invention is effective as a nutritional supplement, either therapeutically or prophylacticly, for example, in preventing the severity or delaying or preventing the onset of a disease.

While there has been described what is presently believed to be the preferred embodiments of the present invention, other and further modifications and changes may be made without departing from the spirit of the invention. All further and other modifications and changes are included that come within the scope of the invention as set forth in the claims. The disclosure of all publications cited above are expressly incorporated by reference in their entireties to the same extent as if each were incorporated by reference individually.

We claim:

1. A composition for supplementing nutritional deficiencies in a patient or person in need thereof, comprising about 2400 IU carotenoids or more, vitamin E, vitamin D, vitamin C, thiamine, riboflavin, niacin, more than 0.8 mg folic acid, pyridoxine, biotin, pantothenic acid, cobalamin, magnesium, manganese, zinc, selenium, chromium, copper, alpha lipoic acid, and about 4 mg lutein or more, wherein said composition is free of any other added minerals and any other added vitamins.

2. The composition of claim **1**, wherein said carotenoids are present in the range of about 2400 IU to about 3600 IU.

3. The composition of claim **1**, wherein said carotenoids comprise at least one carotenoid selected from the group consisting of alpha-carotene, beta-carotene, cryptoxanthin, lutein, and zeaxanthin.

4. The composition of claim **3**, wherein said carotenoid is present in the amount of about 3000 IU.

5. The composition of claim **1**, wherein said vitamin E is present in the range of about 80 IU to about 120 IU.

6. The composition of claim **1**, wherein said vitamin E comprises d-alpha tocopheryl succinate.

7. The composition of claim **6**, wherein said vitamin E is present in the amount of about 100 IU.

8. The composition of claim **1**, wherein said vitamin D is in the range of about 320 IU to about 480 IU.

9. The composition of claim **1**, wherein said vitamin D comprises vitamin D_3.

10. The composition of claim **9**, wherein said vitamin D is present in the amount of about 400 IU.

11. The composition of claim **1**, wherein said vitamin C is in the range of about 240 mg to about 360 mg.

12. The composition of claim **1**, wherein said vitamin C is in the amount of about 300 mg.

13. The composition of claim **1**, wherein said thiamine is in the range of about 16 mg to about 24 mg.

14. The composition of claim **1**, wherein said thiamine comprises thiamine HCl.

15. The composition of claim **14**, wherein said thiamine is present in the amount of about 20 mg.

16. The composition of claim **1**, wherein said riboflavin is present in the range of about 4 mg to about 6 mg.

17. The composition of claim **1**, wherein said riboflavin is present in the amount of about 5 mg.

18. The composition of claim **1**, wherein said niacin is present in the range of about 20 mg to about 30 mg.

19. The composition of claim **1**, wherein said niacin comprises niacinamide.

20. The composition of claim **19**, wherein said niacin is present in the amount of about 25 mg.

21. The composition of claim **1**, wherein folic acid is present in the range of more than 0.8 mg to about 1.0 mg.

22. The composition of claim **1**, wherein said folic acid is present in the amount of about 1 mg.

23. The composition of claim **1**, wherein said pyridoxine is present in the range of about 20 mg to about 30 mg.

24. The composition of claim **1**, wherein said pyridoxine comprises pyridoxine HCl.

25. The composition of claim **24**, wherein said pyridoxine is present in the amount of about 25 mg.

26. The composition of claim **1**, wherein said biotin is present in the range of about 80 μg to about 120 μg.

27. The composition of claim **1**, wherein said biotin is present in the amount of about 100 μg.

28. The composition of claim **1**, wherein said pantothenic acid is present in the range of about 12 mg to about 18 mg.

29. The composition of claim **1**, wherein said pantothenic acid comprises calcium pantothenate.

30. The composition of claim **29**, wherein said pantothenic acid is present in the amount of about 15 mg.

31. The composition of claim **1**, wherein said cobalamin is present in the range of about 40 μg to about 60 μg.

32. The composition of claim **1**, wherein said cobalamin comprises cyanocobalamin.

33. The composition of claim **32**, wherein said cobalamin is present in the amount of about 50 μg.

34. The composition of claim **1**, wherein said magnesium is present in the range of about 40 mg to about 60 mg.

35. The composition of claim **1**, wherein said magnesium comprises magnesium oxide.

36. The composition of claim **35**, wherein said magnesium is present in the amount of about 50 mg.

37. The composition of claim **1**, wherein said manganese is present in the range of about 1.2 mg to about 1.8 mg.

38. The composition of claim **1**, wherein said manganese comprises manganese sulfate.

39. The composition of claim **38**, wherein said manganese is present in the amount of about 1.5 mg.

40. The composition of claim **1**, wherein said zinc is present in the range of about 20 mg to about 30 mg.

41. The composition of claim **1**, wherein said zinc comprises zinc oxide.

42. The composition of claim **41**, wherein said zinc is present in the amount of about 25 mg.

43. The composition of claim **1**, wherein said selenium is present in the range of about 80 μg to about 120 μg.

44. The composition of claim **1**, wherein said selenium comprises sodium selenate.

45. The composition of claim **44**, wherein said selenium is present in the amount of about 100 μg.

46. The composition of claim **1**, wherein said chromium is present in the range of about 40 μg to about 60 μg.

47. The composition of claim **1**, wherein said chromium comprises chromium chloride.

48. The composition of claim **47**, wherein said chromium is present in the amount of about 50 μg.

49. The composition of claim **1**, wherein said copper is present in the range of about 1.2 mg to about 1.8 mg.

50. The composition of claim **1**, wherein said copper comprises cupric sulfate.

51. The composition of claim **50**, wherein said copper is present in the amount of about 1.5 mg.

52. The composition of claim **1**, wherein said alpha lipoic acid is present in the range of about 12 mg to about 18 mg.

53. The composition of claim **1**, wherein said alpha lipoic acid is present in the amount of about 15 mg.

54. The composition of claim **1**, wherein said lutein is in the range of about 4 mg to about 6 mg.

55. The composition of claim **1**, wherein said lutein is present in the amount of about 5 mg.

56. A method for supplementing nutritional deficiencies in a patient or person in need thereof, comprising administering to a patient or a person a composition comprising about 2400 IU carotenoids or more, vitamin E, vitamin D, vitamin C, thiamine, riboflavin, niacin, more than 0.8 mg folic acid, pyridoxine, biotin, pantothenic acid, cobalamin, magnesium, manganese, zinc, selenium, chromium, copper, alpha lipoic acid, and about 4 mg lutein or more, wherein said composition is free of any other added minerals and any other added vitamins.

57. The method of claim **56**, wherein said carotenoids are present in the range of about 2400 IU to about 3600 IU.

58. The method of claim **56**, wherein said carotenoids comprise at least one carotenoid selected from the group consisting of alpha-carotene, beta-carotene, cryptoxanthin, lutein, and zeaxanthin.

59. The method of claim **58**, wherein said carotenoid is present in the amount of about 3000 IU.

60. The method of claim **56**, wherein said vitamin E is present in the range of about 80 IU to about 120 IU.

61. The method of claim **56**, wherein said vitamin E comprises d-alpha tocopheryl succinate.

62. The method of claim **61**, wherein said vitamin E is present in the amount of about 100 IU.

63. The method of claim **56**, wherein said vitamin D is present in the range of about 320 IU to about 480 IU.

64. The method of claim **56**, wherein said vitamin D comprises D_3.

65. The method of claim **64**, wherein said vitamin D is present in the amount of about 400 IU.

66. The method of claim **56**, wherein said vitamin C is present in the range of about 240 mg to about 360 mg.

67. The method of claim **56**, wherein said vitamin C is present in the amount of about 300 mg.

68. The method of claim **56**, wherein said thiamine is present in the range of about 16 mg to about 24 mg.

69. The method of claim **56**, wherein said thiamine comprises thiamine HCl.

70. The method of claim **69**, wherein said thiamine is present in the amount of about 20 mg.

71. The method of claim **56**, wherein said riboflavin is present in the range of about 4 mg to about 6 mg.

72. The method of claim **56**, wherein said riboflavin is in the amount of about 5 mg.

73. The method of claim **56**, wherein said niacin is present in the range of about 20 mg to about 30 mg.

74. The method of claim **56**, wherein said niacin comprises niacinamide.

75. The method of claim **74**, wherein said niacin is present in the amount of about 25 mg.

76. The method of claim **56**, wherein folic acid is present in the range of more than 0.8 mg to about 1.0 mg.

77. The method of claim **56**, wherein said folic acid is present in the amount of about 1 mg.

78. The method of claim **56**, wherein said pyridoxine is present in the range of about 20 mg to about 30 mg.

79. The method of claim **56**, wherein said pyridoxine comprises pyridoxine HCl.

80. The method of claim **79**, wherein said pyridoxine is present in the amount of about 25 mg.

81. The method of claim **56**, wherein said biotin is present in the range of about 80 μg to about 120 μg.

82. The method of claim **56**, wherein said biotin is present in the amount of about 100 μg.

83. The method of claim **56**, wherein said pantothenic acid is present in the range of about 12 mg to about 18 mg.

84. The method of claim **56**, wherein said pantothenic acid comprises calcium pantothenate.

85. The method of claim **84**, wherein said pantothenic acid is present in the amount of about 15 mg.

86. The method of claim **56**, wherein said cobalamin is present in the range of about 40 μg to about 60 μg.

87. The method of claim **56**, wherein said cobalamin comprises cyanocobalamin.

88. The method of claim **87**, wherein said cobalamin is present in the amount of about 50 μg.

89. The method of claim **56**, wherein said magnesium is present in the range of about 40 mg to about 60 mg.

90. The method of claim **56**, wherein said magnesium comprises magnesium oxide.

91. The method of claim **90**, wherein said magnesium is present in the amount of about 50 mg.

92. The method of claim **56**, wherein said manganese is present in the range of about 1.2 mg to about 1.8 mg.

93. The method of claim **56**, wherein said manganese comprises manganese sulfate.

94. The method of claim **93**, wherein said manganese is present in the amount of about 1.5 mg.

95. The method of claim **56**, wherein said zinc is present in the range of about 20 mg to about 30 mg.

96. The method of claim **56**, wherein said zinc comprises zinc oxide.

97. The method of claim **96**, wherein said zinc is present in the amount of about 25 mg.

98. The method of claim **56**, wherein said selenium is present in the range of about 80 μg to about 120 μg.

99. The method of claim **56**, wherein said selenium comprises sodium selenate.

100. The method of claim **99**, wherein said selenium is present in the amount of about 100 μg.

101. The method of claim **56**, wherein said chromium is present in the range of about 40 μg to about 60 μg.

102. The method of claim **56**, wherein said chromium comprises chromium chloride.

103. The method of claim **102**, wherein said chromium is present in the amount of about 50 μg.

104. The method of claim **56**, wherein said copper is present in the range of about 1.2 mg to about 1.8 mg.

105. The method of claim **56**, wherein said copper comprises cupric sulfate.

106. The method of claim **105**, wherein said copper is present in the amount of about 1.5 mg.

107. The method of claim **56**, wherein said alpha lipoic acid is present in the range of about 12 mg to about 18 mg.

108. The method of claim **56**, wherein said alpha lipoic acid is present in the amount of about 15 mg.

109. The method of claim **56**, wherein said lutein is present in the range of about 4 mg to about 6 mg.

110. The method of claim **56**, wherein said lutein is present in the amount of about 5 mg.

* * * * *

Exhibit D

Complaint of Breckenridge Pharmaceutical Filed January 7, 2009 (abridged)

Civil Action No. 09-80015 S.D. Fla.

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF FLORIDA

CASE NO._____

BRECKENRIDGE PHARMACEUTICAL, INC.,
a Florida corporation,

Plaintiff,

v.

EVERETT LABORATORIES, INC.,
a New Jersey Corporation,

Defendant.

09-80015-Civ-MARRA/JOHNSON

COMPLAINT

Breckenridge Pharmaceutical, Inc., by and through its attorneys, states as follows for its Complaint against Defendant Everett Laboratories, Inc.:

The Parties

1. Plaintiff Breckenridge Pharmaceutical, Inc. ("Breckenridge") is a corporation organized and existing under the laws of the State of Florida, with its principal place of business at 1141 South Rogers Circle, Suite 3, Boca Raton, Florida 33487.

2. Breckenridge is in the business of developing, marketing and selling prescription products to retailers, wholesalers, distributors, and other purchasers of such products nationwide.

3. Defendant Everett Laboratories, Inc. ("Everett") is a corporation organized and existing under the laws of the State of New Jersey, with a principal place of business at 29 Spring Street, West Orange, New Jersey.

4. Everett markets and sells prescription products to retailers, wholesalers, distributors, and other purchasers of such products nationwide, including within the Southern District of Florida.

Jurisdiction And Venue

5. This is an action for a declaratory judgment pursuant to 28 U.S.C. § 2201, for the purpose of determining a case of actual controversy between the parties, as hereinafter more fully appears. Jurisdiction is proper under 28 U.S.C. § 1338(a) because the subject of the action is the invalidity and non-infringement of two United States patents, arising under an Act of Congress relating to patents, as well as the invalidity and non-infringement of a copyright, arising under the Copyright Act.

6. Venue is proper in this District pursuant to 28 U.S.C. §§ 1391 and 1400, because Everett regularly sells its products in this District.

STATEMENT OF FACTS

The Competing Prescription Multi-Vitamin And Mineral Products

7. Prescription products with the same active ingredients, dosage form, and strength are sometimes available from more than one supplier ("Multisource" products). Typically, the market for a particular Multisource product begins with one established brand-name product, which is eventually joined by lower-cost, Multisource alternatives.

8. Breckenridge competes in the Multisource market by developing and selling lower-cost, Multisource alternatives to established, higher-priced brand products.

9. Before introducing any new pharmaceutical product into the marketplace, Breckenridge invests significant resources to ensure that the formulation, testing, and manufacture of each of its products complies both with internal quality-control release standards as well as with all applicable U.S. Food and Drug Administration regulations, including current Good Manufacturing Practices. Breckenridge also conducts due diligence that includes the

review and analysis of any intellectual property that may potentially be relevant to the introduction of a new pharmaceutical product.

10. Everett markets a prescription multi-vitamin and mineral (collectively, "multivitamin") product under the name Strovite® Advance.

11. On January 7, 2009, under the name Nutravance, Breckenridge began to market and sell its lower-cost Multisource multivitamin product in competition with Everett's Strovite® Advance.

12. In order to compete for this market, Multisource competitors to a brand product must indicate on their labels the same active ingredients in the same amounts as shown on the label for the brand product.

13. Accordingly, Breckenridge's Nutravance contains the same active ingredients in the same amounts as Everett's Strovite® Advance, and so indicates on its label.

The Patents At Issue

14. United States Patent No. 6,660,293 ("the '293 patent"), entitled "Compositions and Methods for Prophylactic and Therapeutic Supplementation of Nutrition in Subjects," was issued on December 9, 2003, to John A. Giordano and Charles Balzer as the inventors. A copy of the '293 patent is attached as Exhibit A.

15. Everett is identified on the '293 patent as the assignee thereof.

16. Both the container and the product insert for Everett's Strovite® Advance are marked with the '293 patent.

17. Accordingly, upon information and belief, Everett will claim that other multivitamin products with the same amounts of the same active ingredients as its Strovite® Advance, including Breckenridge's Nutravance, infringe the '293 patent.

18. A continuation of the application which issued as the '293 patent was filed on October 14, 2003. This continuation application issued on March 8, 2005, as United States Patent No. 6,863,904 ("the '904 patent"), also entitled "Compositions and Methods for Prophylactic and Therapeutic Supplementation of Nutrition in Subjects," with John A. Giordano and Charles Balzer named as the inventors. A copy of the '904 patent is attached as Exhibit B.

19. As with the '293 patent, Everett is identified on the '904 patent as the assignee thereof.

20. Both the container and the product insert for Everett's Strovite® Advance are also marked with the '904 patent.

21. Accordingly, upon information and belief, Everett will claim that other multivitamin products with the same amounts of the same active ingredients as its Strovite® Advance, including Breckenridge's Nutravance, infringe the '904 patent.

Everett's Copyright

22. Upon information and belief, Everett owns one or more United States copyright registrations for the product insert used for its Strovite® Advance product, including Registration No. TX 0006214099, which is identified in the online database of the United States Copyright Office as "Strovite advance product insert" and which is listed as being owned by Everett Laboratories, Inc.

Everett's Prior Lawsuits Against Breckenridge And Others Concerning Its Multivitamin Products, And The Current Dispute

23. Over the past several years, Everett has filed a succession of lawsuits against competitors that marketed lower-cost Multisource alternatives to its multivitamin products, alleging multiple causes of action including, *inter alia*, patent infringement, copyright infringement, and unfair competition. *See Everett Laboratories, Inc. v. Rising Pharmaceuticals,*

Inc., No. 2:04-cv-01414-DMC-MF (D. N.J.) and No. 2:04-cv-05673-JAP-MCA (D. N.J.); *Everett Laboratories, Inc. v. Vertical Pharmaceuticals, Inc.*, No. 2:05-cv-05926-DRD-MAS (D. N.J.); and *Everett Laboratories, Inc. v. River's Edge Pharmaceuticals, Inc.*, No. 2:08-cv-000075-KSH-PS (D. N.J.).

24. Most recently, on June 24, 2008, Everett filed a lawsuit against Breckenridge based on Breckenridge's introduction of a multivitamin product that competed against Everett's Vitafol-OB multivitamin product: *Everett Laboratories, Inc. v. Breckenridge Pharmaceutical, Inc.*, No. 2:08-cv-03156 (JLL)(CCC) (D. N.J.). In that action, Everett obtained a preliminary injunction concerning the specific product at issue in that case. However, Breckenridge has appealed the ruling, based on errors in the trial court's assessment of Everett's showing of likelihood of success on the merits and irreparable harm.

25. Based on the foregoing, the totality of the circumstances shows that an actual and substantial controversy exists between the parties, having adverse legal interests, for reasons including but not limited to:

a. Everett has filed a succession of lawsuits to block competition by Multisource alternatives to its own multivitamin products;

b. After Breckenridge earlier this year introduced a Multisource alternative to compete with Everett's multivitamin product Vitafol-OB, Everett filed such a lawsuit against Breckenridge alleging, *inter alia*, patent infringement and copyright infringement;

c. Breckenridge has now introduced its Nutravance multivitamin product, which competes directly with Everett's Strovite® Advance multivitamin product;

d. Everett's product labeling for its Strovite® Advance indicates that it is covered by both the '293 patent and the '904 patent;

e. Everett has also registered a copyright for the product insert of its Strovite® Advance; and

f. Breckenridge maintains that it does not need a license to market its Nutravance multivitamin product, that it does not infringe any valid patent claim, and that its product information inserts do not infringe any valid copyright;

as a consequence of which, Breckenridge has a reasonable apprehension of a lawsuit by Everett.

26. Accordingly, there is an actual controversy between the parties that may be adjudicated by way of declaratory judgment pursuant to 28 U.S.C. § 2201.

COUNT I
Declaration of Invalidity of the '293 Patent

27. Breckenridge incorporates the allegations of the preceding paragraphs as though fully set forth herein.

28. The '293 patent is invalid for failure to comply with the statutory requirements of patentability under Title 35 of the United States Code, including but not limited to 35 U.S.C. §§ 101, 102, 103, and 112, and/or the requirements of Title 37 of the Code of Federal Regulations.

29. Accordingly, Breckenridge is entitled to a declaration that the '293 patent is invalid.

COUNT II
Declaration of Invalidity of the '904 Patent

30. Breckenridge incorporates the allegations of the preceding paragraphs as though fully set forth herein.

31. The '904 patent is invalid for failure to comply with the statutory requirements of patentability under Title 35 of the United States Code, including but not limited to 35 U.S.C. §§ 101, 102, 103, and 112, and/or the requirements of Title 37 of the Code of Federal Regulations.

32. Accordingly, Breckenridge is entitled to a declaration that the '904 patent is invalid.

COUNT III
Declaration of Non-Infringement of the Patents-in-Suit

33. Breckenridge incorporates the allegations of the preceding paragraphs as though fully set forth herein.

34. Breckenridge's Nutravance does not directly infringe any valid claim of the '293 patent or the '904 patent, either literally or under the doctrine of equivalents; nor does Breckenridge, by its sale of Nutravance, indirectly infringe by inducing infringement or contributing to infringement of any valid claim of the '293 patent or the '904 patent.

35. Accordingly, Breckenridge is entitled to a declaration that it does not, by its marketing and sale of its Nutravance multivitamin product, directly or indirectly infringe any valid claim of the '293 patent or the '904 patent.

COUNT IV
Declaration of Invalidity of Copyright

36. Breckenridge incorporates the allegations of the preceding paragraphs as though fully set forth herein.

37. Everett's Strovite® Advance product insert that is the subject of the copyright

registered by Everett as United States Copyright Registration No. TX0006214099, and possibly the subject of other copyright registrations not currently known to Breckenridge, is a functional list or description of the ingredients contained in the product and the basic instructions necessary for proper use of the product, which does not contain sufficiently original material to constitute an original work of authorship under Section 102(a) of the United States Copyright Act, 17 U.S.C. § 102(a).

38. Everett's Strovite® Advance product insert that is the subject of the copyright registered by Everett as United States Copyright Registration No. TX0006214099, and possibly the subject of other copyright registrations not currently known to Breckenridge, is a functional list or description of the ingredients contained in the product and the basic instructions necessary for proper use of the product, which constitutes an idea, procedure, process, system, method of operation, concept, principle, or discovery not entitled to copyright protection pursuant to Section 102(b) of the United States Copyright Act, 17 U.S.C. § 102(b).

39. Accordingly, Breckenridge is entitled to a declaration that Everett does not own any copyright rights in the Strovite® Advance product insert, and that any copyright registration which Everett has obtained for the Strovite® Advance product insert, including United States Copyright Registration No. TX0006214099, is invalid.

COUNT V
Declaration of Non-Infringement of Copyright Based on Fair Use

40. Breckenridge incorporates the allegations of the preceding paragraphs as though fully set forth herein.

41. Everett's Strovite® Advance product insert that is the subject of the copyright registered by Everett as United States Copyright Registration No. TX0006214099, and possibly the subject of other copyright registrations not currently known to Breckenridge, is

a functional list or description of the ingredients contained in the product and the basic instructions necessary for proper use of the product, such that Breckenridge's alleged copying and use of the information contained on that product insert in order to fairly and accurately provide the same information to its customers regarding the content and use of its own product is a fair use under Section 107 of the United States Copyright Act, 17 U.S.C. § 102(b).

42. Accordingly, Breckenridge is entitled to a declaration that the product insert for its Nutravance product does not infringe any copyright rights that Everett may claim in the Strovite® Advance product insert, including any rights claimed to be derived from United States Copyright Registration No. TX0006214099 and any other copyright registrations that Everett may have obtained for the Strovite® Advance product insert.

WHEREFORE, Breckenridge requests that the Court:

(a) Enter judgment declaring that United States Patent No. 6,660,293 is invalid;

(b) Enter judgment declaring that United States Patent No. 6,863,904 is invalid;

(c) Enter judgment declaring that Breckenridge does not, by its marketing and sale of its Nutravance multivitamin product, directly or indirectly infringe any valid claim of United States Patent No. 6,660,293 or No. 6,863,904;

(d) Enter judgment declaring invalid Everett's copyright to the Strovite® Advance product insert, registered by Everett as United States Copyright Registration No. TX0006214099 and possibly other copyright registrations as well;

(e) Enter judgment declaring that any copying and use by Breckenridge of the information contained on the product insert for Everett's Strovite® Advance constitutes a fair use;

(f) Enter an order enjoining Everett and its privies from asserting either United States Patent No. 6,660,293 or No. 6,863,904, or any copyright on the product insert for Everett's Strovite® Advance, against Breckenridge and/or its privies on the basis of Breckenridge's Nutravance product;

(g) Declare this case exceptional and enter an order awarding attorneys' fees and expenses to Breckenridge pursuant to 35 U.S.C. § 285;

(h) Enter an order granting Breckenridge the costs of this litigation; and

(i) Enter an order granting Breckenridge such other and additional relief against Everett as may be just and proper in the circumstances.

DEMAND FOR TRIAL BY JURY

Pursuant to Rule 38(b) of the Federal Rules of Civil Procedure, Breckenridge demands a trial by jury of all issues properly triable to a jury in this case.

Dated: January 7, 2009

BUCKINGHAM, DOOLITTLE & BURROUGHS, LLP

BY: Jennifer E Simpson

Robert E. Pershes, Esquire
Florida Bar No. 301906
lpershes@bdblaw.com
L.A. Perkins, Esquire
Florida Bar No. 100153
lperkins@bdblaw.com
Jennifer E. Simpson, Esquire
Florida Bar No. 0697354
jsimpson@bdblaw.com
5355 Town Center Road, Suite 900
Boca Raton, Florida 33486-1069
Telephone: (561) 241-0414
Facsimile: (561) 241-9766

«BOCA:190695_v2/49684-0085»

Exhibit E

TX 6-214-099

Certificate of Registration For Strovite® Advance Insert

Certificate of Registrati .

This Certificate issued under the seal of the Copyright Office in accordance with title 17, United States Code, attests that registration has been made for the work identified below. The information on this certificate has been made a part of the Copyright Office records.

Marybeth Peters

Register of Copyrights, United States of America

Form TX
For a Nondramatic Literary Work
UNITED STATES COPYRIGHT OFFICE

TX 6-214-099

EFFECTIVE DATE OF REGISTRATION
AUG 17 2004
Month Day Year

ARATE CONTINUATION SHEET

1 TITLE OF THIS WORK ▼
STROVITE ADVANCE Product Insert

PREVIOUS OR ALTERNATIVE TITLES ▼

PUBLICATION AS A CONTRIBUTION If this work was published as a contribution to a periodical, serial, or collection, give information about the collective work in which the contribution appeared. Title of Collective Work ▼

If published in a periodical or serial give: Volume ▼ Number ▼ Issue Date ▼ On Pages ▼

2 a NAME OF AUTHOR ▼
Everett Laboratories Inc

DATES OF BIRTH AND DEATH
Year Born ▼ Year Died ▼

Was this contribution to the work a "work made for hire"?
☑ Yes
☐ No

AUTHOR S NATIONALITY OR DOMICILE
Name of Country
OR { Citizen of ▶ ____
Domiciled in ▶ ____

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If the answer to either of these questions is "Yes," see detailed instructions.
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3 a YEAR IN WHICH CREATION OF THIS WORK WAS COMPLETED
This information must be given in all cases
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b DATE AND NATION OF FIRST PUBLICATION OF THIS PARTICULAR WORK
Complete this information ONLY if this work has been published.
Month ▶ 05 Day ▶ 1 Year ▶ 2001
USA ◀ Nation

4 COPYRIGHT CLAIMANT(S) Name and address must be given even if the claimant is the same as the author given in space 2 ▼
Everett Laboratories Inc
29 Spring Street
West Orange NJ 07052 USA

See instructions before completing this space

TRANSFER If the claimant(s) named here in space 4 is (are) different from the author(s) named in space 2 give a brief statement of how the claimant(s) obtained ownership of the copyright ▼

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