(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 October 2004 (28.10.2004)

PCT

(10) International Publication Number
WO 2004/091573 A1

(51) International Patent Classification[7]: A61K 9/00, 38/16, 31/05, 31/045

(21) International Application Number: PCT/US2004/006799

(22) International Filing Date: 4 March 2004 (04.03.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/451,847 4 March 2003 (04.03.2003) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *with amended claims*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/091573 A1

(54) Title: COMBINATION THERAPY WITH GLATIRAMER ACETATE AND ALPHACALCIDOL FOR THE TREATMENT OF MULTIPLE SCLEROSIS

(57) Abstract: The subject invention provides a method of treating a subject afflicted with a form of multiple sclerosis comprising periodically administering to the subject an amount of glatiramer acetate and an amount of alphacalcidol, wherein the amounts when taken together are effective to alleviate a symptom of the form of multiple sclerosis in the subject so as to thereby treat the subject. The subject invention also provides a package comprising glatiramer acetate, alphacalcidol and instructions for use of the together to alleviate a symptom of a form of multiple sclerosis in a subject. Additionally, the subject invention provides a pharmaceutical composition comprising an amount of glatiramer acetate and an amount of alphacalcidol, wherein the amounts when taken together are effective to alleviate a symptom of a form of multiple sclerosis in a subject. The subject invention further provides a pharmaceutical combination comprising separate dosage forms of an amount of glatiramer acetate and an amount of alphacalcidol, which combination is useful to alleviate a symptom of a form of multiple sclerosis in a subject.

COMBINATION THERAPY WITH GLATIRAMER ACETATE AND ALPHACALCIDOL FOR THE TREATMENT OF MULTIPLE SCLEROSIS

The present application claims the benefit of U.S. Provisional Application No. 60/451,847, filed March 4, 2003, which is incorporated by reference herein.

Throughout this application, various events are referenced in parenthesis. Full citations for these publications may be found listed in alphabetical order at the end of the specification immediately preceding the claims. The disclosures of these publications in their entireties are hereby incorporated by reference into this application in order to more fully describe the state of the art to which this invention pertains.

Field of the Invention

The subject invention relates to combination therapy for treating multiple sclerosis.

Background of the Invention

One of the more common neurologic diseases in human adults is multiple sclerosis. This condition is a chronic, inflammatory CNS disease characterized pathologically by demyelination. There are five main forms of multiple sclerosis: 1) benign multiple sclerosis; 2) relapsing-remitting multiple sclerosis (RR-MS); 3) secondary progressive multiple sclerosis (SP-MS); 4) primary progressive multiple sclerosis (PP-MS); and 5) progressive-relapsing multiple sclerosis (PR-MS). Benign multiple sclerosis is characterized by 1-2 exacerbations with complete recovery, no lasting disability and no disease progression for 10-15 years after the initial onset. Benign multiple sclerosis may, however, progress into other forms of multiple sclerosis. Patients suffering from RR-MS experience sporadic exacerbations or relapses, as well as periods of remission. Lesions and evidence of axonal loss may or may not be visible on MRI for patients with RR-MS. SP-MS may evolve from RR-MS. Patients

afflicted with SP-MS have relapses, a diminishing degree of recovery during remissions, less frequent remissions and more pronounced neurological deficits than RR-MS patients. Enlarged ventricles, which are markers for atrophy of the corpus callosum, midline center and spinal cord, are visible on MRI of patients with SP-MS. PP-MS is characterized by a steady progression of increasing neurological deficits without distinct attacks or remissions. Cerebral lesions, diffuse spinal cord damage and evidence of axonal loss are evident on the MRI of patients with PP-MS. PR-MS has periods of acute exacerbations while proceeding along a course of increasing neurological deficits without remissions. Lesions are evident on MRI of patients suffering from PR-MS (Multiple sclerosis: its diagnosis, symptoms, types and stages).

Researchers have hypothesized that multiple sclerosis is an autoimmune disease (Compston; Hafler and Weiner; Olsson). An autoimmune hypothesis is supported by the experimental allergic encephalomyelitis (EAE) model of multiple sclerosis, where the injection of certain myelin components into genetically susceptible animals leads to T cell-mediated CNS demyelination (Parkman). Another theory regarding the pathogenesis of multiple sclerosis is that a virus, bacteria or other agent, precipitates an inflammatory response in the CNS, which leads to either direct or indirect ("bystander") myelin destruction, potentially with an induced autoimmune component (Lampert; Martyn). Another experimental model of multiple sclerosis, Theiler's murine encephalomyelitis virus (TMEV)(Dal Canto and Lipton; Rodriguez et al.), supports the theory that a foreign agent initiates multiple sclerosis. In the TMEV model, injection of the virus results in spinal cord demyelination.

Glatiramer acetate (GA), also known as Copolymer-1, has been shown to be effective in treating multiple sclerosis (MS) (Lampert, P.W.). Daily subcutaneous injections of glatiramer acetate (20 mg/injection) reduce relapse rates, progression of disability, appearance of new lesions by magnetic resonance imaging (MRI),

(Johnson, K.P. et al.) and appearance of "black holes" (Filippi, M. et al.).

COPAXONE® is the brand name for a formulation containing glatiramer acetate as the active ingredient. Glatiramer acetate is approved for reducing the frequency of relapses in relapsing-remitting multiple sclerosis. Glatiramer acetate consists of the acetate salts of synthetic polypeptides containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine, and L-lysine with an average molar fraction in COPAXONE® of 0.141, 0.427, 0.095 and 0.338, respectively. In COPAXONE®, the average molecular weight of the glatiramer acetate is 4,700-11,000 daltons. Chemically, glatiramer acetate is designated L-glutamic acid polymer with L-alanine, L-lysine and L-tyrosine, acetate (salt). Its structural formula is:

$$(Glu, Ala, Lys, Tyr)_x \cdot CH_3COOH$$
$$(C_5H_9NO_4 \cdot C_3H_7NO_2 \cdot C_6H_{14}N_2O_2 \cdot C_9H_{11}NO_3)_x \cdot \chi C_2H_4O_2$$

CAS - 147245-92-9.

The recommended dosing schedule of COPAXONE® for relapsing-remitting multiple sclerosis is 20 mg per day injected subcutaneously (Physician's Desk Reference, 2003; see also U.S. Patent Nos. 3,849,550; 5,800,808; 5,858,964, 5,981,589; 6,048,898; 6,054,430; 6,214,791; 6,342,476; and 6,362,161, all of which are hereby incorporated by reference).

Alphacalcidol is 1α-hydroxycholecaliferol (Paterson; Treatment with active vitamin D (alphacalcidol) in patients with mild primary hyperparathyroidism). After absorption into the body, alphacalcidol is converted into 1α,25-dihydroxycholecalciferol (Product Description). Alphacalcidol is commercially available under the tradename, Alpha D_3® (Alpha D_3). Alphacalcidol is indicated for conditions in which calcium and/or phosphate metabolism (DeLuca, H.F.; Product Description) is impaired such as renal bone disease, osteoporosis, osteopenia,

hypoparathyriodism and hyperparathyroidism with bone disease, rickets, osteomalacia and renal osteodystrophy (Product Description). The recommended dose for alpacalcidol for all of the afore-mentioned indications except osteoporosis is 1 µg/day for adults, 0.5 µg/day for the elderly and 1 µg/day for children 20 kg and over except for renal osteodystrophy, for which the recommended dose is 0.04 to 0.08 µg/kg/day. The dose for osteoporosis has not been established, but clinical trials have used 0.5 - 1.0 µg/day. It is recommended that the dose be adjusted according to the biochemical response in order to avoid hypercalcemia (Product Description). Some have suggested that alphacalcidol be taken in the morning (Commonly Taken Drugs (for Kidney Failure)).

It has been suggested that 1α,25-dihydroxycholecalciferol prevents the development of murine experimental autoimmune encephalomyelitis (EAE), a model of multiple sclerosis (Cantorna, M.T., et al.; Lemire, J.M and Archer, D.C.). It has also been suggested that 1α,25-dihydroxycholecalciferol prevents the progression of murine EAE when administered after the induction of EAE (Cantorna, M.T., et al.).

The administration of two drugs to treat a given condition, such as a form of multiple sclerosis, raises a number of potential problems. *In vivo* interactions between two drugs are complex. The effects of any single drug are related to its absorption, distribution, and elimination. When two drugs are introduced into the body, each drug can affect the absorption, distribution, and elimination of the other and hence, alter the effects of the other. For instance, one drug may inhibit, activate or induce the production of enzymes involved in a metabolic route of elimination of the other drug (Guidance for Industry. *In vivo* drug metabolism/drug interaction studies - study design, data analysis, and recommendations for dosing and labeling). Thus, when two drugs are administered to treat the

same condition, it is unpredictable whether each will complement, have no effect on, or interfere with, the therapeutic activity of the other in a human subject.

Not only may the interaction between two drugs affect the intended therapeutic activity of each drug, but the interaction may increase the levels of toxic metabolites (Guidance for Industry. *In vivo* drug metabolism/drug interaction studies - study design, data analysis, and recommendations for dosing and labeling). The interaction may also heighten or lessen the side effects of each drug. Hence, upon administration of two drugs to treat a disease, it is unpredictable what change will occur in the negative side profile of each drug.

Additionally, it is accurately difficult to predict when the effects of the interaction between the two drugs will become manifest. For example, metabolic interactions between drugs may become apparent upon the initial administration of the second drug, after the two have reached a steady-state concentration or upon discontinuation of one of the drugs (Guidance for Industry. *In vivo* drug metabolism/drug interaction studies - study design, data analysis, and recommendations for dosing and labeling).

Thus, the success of one drug or each drug alone in an *in vitro* model, an animal model, or in humans, may not correlate into efficacy when both drugs are administered to humans.

In accordance with the subject invention, glatiramer acetate and alphacalcidol are effective in combination to treat a form of multiple sclerosis, specifically, relapsing-remitting multiple sclerosis.

Summary of the Invention

The subject invention provides a method of treating a subject afflicted with a form of multiple sclerosis comprising periodically administering to the subject an amount of glatiramer acetate and an amount of alphacalcidol, wherein the amounts when taken together are effective to alleviate a symptom of the form of multiple sclerosis in the subject so as to thereby treat the subject.

In addition, the subject invention provides a package comprising

i) a first pharmaceutical composition comprising an amount of glatiramer acetate and a pharmaceutically acceptable carrier;

ii) a second pharmaceutical composition comprising an amount of alphacalcidol and a pharmaceutically acceptable carrier; and

iii) instructions for use of the first and second pharmaceutical compositions together to alleviate a symptom of a form of multiple sclerosis in a subject.

The subject invention further provides a pharmaceutical composition comprising an amount of glatiramer acetate and an amount of alphacalcidol, wherein the amounts when taken together are effective to alleviate a symptom of a form of multiple sclerosis in a subject.

Detailed Description of the Invention

The subject invention provides a method of treating a subject afflicted with a form of multiple sclerosis comprising periodically administering to the subject an amount of glatiramer acetate and an amount of alphacalcidol, wherein the amounts when taken together are effective to alleviate a symptom of the form of multiple sclerosis in the subject so as to thereby treat the subject.

In one embodiment, the form of multiple sclerosis is relapsing-remitting multiple sclerosis.

In another embodiment, the subject is a human being.

In a further embodiment, each of the amount of glatiramer acetate when taken alone, and the amount of alphacalcidol when taken alone is effective to alleviate the symptom of the form of multiple sclerosis.

In an embodiment, either the amount of glatiramer acetate when taken alone, the amount of alphacalcidol when taken alone or each such amount when taken alone is not effective to alleviate the symptom of the form of multiple sclerosis.

In yet another embodiment, the symptom is the frequency of relapses, the frequency of clinical exacerbation, or the accumulation of physical disability.

In one embodiment, the amount of glatiramer acetate may be 10 to 80 mg; or 12 to 70 mg; or 14 to 60 mg; or 16 to 50 mg; or 18 to 40 mg; or 20 to 30 mg; or 20 mg.

For each amount of glatiramer acetate, the amount of alphacalcidol may be 0.1 mg to 10 mg; or 0.25 mg to 7.5 mg; or

0.5 mg to 5 mg; or 0.75 to 2.5 mg; or 1 mg to 1.5 mg; or 1 mg. Alternatively, for each amount of glatiramer acetate, the amount of alphacalcidol may be 0.01 µg to 5 µg; or 0.05 µg to 4 µg; or 0.1 µg to 3 µg; or 0.2 µg to 2 µg; or 0.25 µg to 1 µg; or 0.5 ug to .75 µg.

Alternatively, the amount of glatiramer acetate may be in the range from 10 to 600 mg/week; or 100 to 550 mg/week; or 150 to 500 mg/week; or 200 to 450 mg/week; or 250 to 400 mg/week; or 300 to 350 mg/week; or 300 mg/week.

In another embodiment, the amount of glatiramer acetate may be in the range from 50 to 150 mg/day; or 60 to 140 mg/day; or 70 to 130 mg/day; or 80 to 120 mg/day; or 90 to 110 mg/day; or 100 mg/day.

Alternatively, the amount of glatiramer acetate may be in the range from 10 to 80 mg/day; or 12 to 70 mg/day; or 14 to 60 mg/day; or 16 to 50 mg/day; or 18 to 40 mg/day; or 19 to 30 mg/day; or 20 mg/day.

In one embodiment, the periodic administration of glatiramer acetate is effected daily.

In another embodiment, the periodic administration of glatiramer acetate is effected twice daily at one half the amount.

In an additional embodiment, the periodic administration of glatiramer acetate is effected once every 3 to 11 days; or once every 5 to 9 days; or once every 7 days; or once every 24 hours.

For each administration schedule of glatiramer acetate, the alphacalcidol may be administered once every 20 to 28 hours; or once every 22 to 26 hours; or once every 24 hours.

In an embodiment, the periodic administration of alphacalcidol is effected in the morning.

In a further embodiment, the administration of the glatiramer acetate substantially precedes the administration of the alphacalcidol.

In an added embodiment, the administration of the alphacalcidol substantially precedes the administration of the glatiramer acetate.

In one embodiment, the glatiramer acetate and the alphacalcidol may be administered for a period of time of at least 4 days. In a further embodiment, the period of time may be 5 days to 5 years; or 10 days to 3 years; or 2 weeks to 1 year; or 1 month to 6 months; or 3 months to 4 months. In yet another embodiment, the glatiramer acetate and the alphacalcidol may be administered for the lifetime of the subject.

The administration of alphacalcidol or glatiramer acetate may each independently be oral, nasal, pulmonary, parenteral, intravenous, intra-articular, transdermal, intradermal, subcutaneous, topical, intramuscular, rectal, intrathecal, intraocular, buccal or by gavage. For alphacalcidol, the preferred route of administration is oral or by gavage. The preferred route of administration for glatiramer acetate is subcutaneous or oral. One of skill in the art would recognize that doses at the higher end of the range may be required for oral administration.

In one embodiment, the administration of the glatiramer acetate may be subcutaneous, intraperitoneal, intravenous, intramuscular, intraocular or oral and the administration of the alphacalcidol may be oral. In another embodiment, the administration of the glatiramer acetate may be subcutaneous and

the administration of the alphacalcidol may be oral.

The subject invention also provides a package comprising

i) a first pharmaceutical composition comprising an amount of glatiramer acetate and a pharmaceutically acceptable carrier;

ii) a second pharmaceutical composition comprising an amount of alphacalcidol and a pharmaceutically acceptable carrier; and

iii) instructions for use of the first and second pharmaceutical compositions together to alleviate a symptom of a form of multiple sclerosis in a subject.

In an embodiment of the package, the amount of glatiramer acetate may be in the range from 10 to 600 mg; or 100 to 550 mg; or 150 to 500 mg; or 200 to 450 mg; or 250 to 400 mg; or 300 to 350 mg; or 300 mg.

In another embodiment of the package, the amount of glatiramer acetate may be in the range from 10 to 80 mg; or 12 to 70 mg; or 14 to 60 mg; or 16 to 50 mg; or 18 to 40 mg; or 19 to 30 mg; or 20 mg.

Alternatively, the amount of glatiramer acetate in the package may be in the range from 50 to 150 mg; or 60 to 140 mg; or 70 to 130 mg; or 80 to 120 mg; or 90 to 110 mg; or 100 mg.

For each amount of glatiramer acetate in the package, the amount of alphacalcidol in the package may be 0.1 mg to 10 mg; or 0.25 mg to 7.5 mg; or 0.5 mg to 5 mg; or 0.75 to 2.5 mg; or 1 mg to 1.5 mg; or 1 mg. Alternatively, for each amount of glatiramer acetate in the package, the amount of alphacalcidol in the package may be 0.01 µg to 5 µg; or 0.05 µg to 4 µg; or 0.1 µg to 3 µg; or 0.2 µg to 2 µg; or 0.25 µg to 1 µg; or 0.5 ug to .75 µg.

The subject invention further provides a pharmaceutical composition comprising an amount of glatiramer acetate and an amount of alphacalcidol, wherein the amounts when taken together are effective to alleviate a symptom of a form of multiple sclerosis in a subject.

In one embodiment of the pharmaceutical composition, each of the amount of glatiramer acetate when taken alone and the amount of alphacalcidol when taken alone is effective to alleviate the symptom of multiple sclerosis.

In another embodiment of the pharmaceutical composition, either of the amount of glatiramer acetate when taken alone, or the amount of alphacalcidol when taken alone or each such amount when taken alone is not effective to alleviate the symptom of multiple sclerosis.

The subject invention further provides a pharmaceutical combination comprising separate dosage forms of an amount of glatiramer acetate and an amount of alphacalcidol, which combination is useful to alleviate a symptom of a form of multiple sclerosis in a subject.

In an embodiment of the pharmaceutical combination, each of the amount of glatiramer acetate when taken alone and the amount of alphacalcidol when taken alone is effective to alleviate the symptom of multiple sclerosis.

In an additional embodiment of the pharmaceutical combination, either of the amount of glatiramer acetate when taken alone, the amount of alphacalcidol when taken alone or each such amount when taken alone is not effective to alleviate the symptom of multiple sclerosis.

In a further embodiment, the pharmaceutical combination may be for simultaneous, separate or sequential use to treat the form of multiple sclerosis in the subject.

Formulations of the invention suitable for oral administration may be in the form of capsules, pills, tablets, powders, granules, or as a solution or a suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion, or as an elixir or syrup, or as pastilles (using an inert base, such as gelatin and glycerin, or sucrose and acacia) and/or as mouth washes and the like, each containing a predetermined amount of the active compound or compounds.

In solid dosage forms of the invention for oral administration (capsules, tablets, pills, dragees, powders, granules and the like), the active ingredient(s) is mixed with one or more pharmaceutically acceptable carriers, such as sodium citrate or dicalcium phosphate, and/or any of the following: fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and/or silicic acid; binders, such as, for example, carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, sucrose and/or acacia; humectants, such as glycerol; disintegrating agents, such as agar-agar, calcium carbonate, calcium phosphate, potato or tapioca starch, alginic acid, certain silicates, and sodium carbonate; solution retarding agents, such as paraffin; absorption accelerators, such as quaternary ammonium compounds; wetting agents, such as, for example, cetyl alcohol and glycerol monostearate; absorbents, such as kaolin and bentonite clay; lubricants, such a talc, calcium stearate, magnesium stearate, solid polyethylene glycols, sodium lauryl sulfate, and mixtures thereof; and coloring agents. In the case of capsules, tablets and pills, the pharmaceutical compositions may also comprise buffering agents. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules using such

excipients as lactose or milk sugars, as well as high molecular weight polyethylene glycols and the like.

Liquid dosage forms for oral administration of the active ingredients include pharmaceutically acceptable emulsions, microemulsions, solutions, suspensions, syrups and elixirs. In addition to the active ingredient(s), the liquid dosage forms may contain inert dilutents commonly used in the art, such as, for example, water or other solvents, solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, and mixtures thereof.

Suspensions, in addition to the active compounds, may contain suspending agents such as ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth, and mixtures thereof.

The pharmaceutical compositions, particularly those comprising glatiramer acetate, may also include human adjuvants or carriers known to those skilled in the art. Such adjuvants include complete Freund's adjuvant and incomplete Freund's adjuvant. The compositions may also comprise wetting agents, emulsifying and suspending agents, sweetening, flavoring, coloring, perfuming and preservative agents.

Glatiramer acetate may be formulated into pharmaceutical compositions with pharmaceutically acceptable carriers, such as water or saline and may be formulated into eye drops. Glatiramer acetate may also be formulated into delivery systems, such as matrix systems.

This invention will be better understood from the Experimental Details which follow. However, one skilled in the art will readily appreciate that the specific methods and results discussed are merely illustrative of the invention as described more fully in the claims which follow thereafter.

In one embodiment, a product containing glatiramer acetate and alphacalcidol as a combined preparation for simultaneous, separate or sequential use in therapy; or to alleviate a symptom of a form of multiple sclerosis.

The use of glatiramer acetate and alphacalcidol for the manufacture of a combined preparation medicament for use to alleviate a symptom of a form of multiple sclerosis, wherein glatiramer acetate and alphacalcidol are administered simultaneously, separately or sequentially.

The administration of alphacalcidol is at least once every 28 hours for each administration of glatiramer acetate; or at least once every 24 hours for each administration of glatiramer acetate; or simultaneous to each administration of glatiramer acetate.

The use of alphacalcidol for the manufacture of a medicament for use to alleviate or to enhance alleviation of a symptom of a form of multiple sclerosis in a patient who is being treated with glatiramer acetate to alleviate the symptom of a form of multiple sclerosis.

Alternatively, the use of alphacalcidol for the manufacture of a medicament for use to alleviate a patient population that is being treated with glatiramer acetate to alleviate the symptom of a form of multiple sclerosis.

Experimental Details

CLINICAL TRIAL OF RELAPSING-REMITTING MULTIPLE SCLEROSIS

The purpose of this trial is to compare the treatment of participants with relapsing-remitting multiple sclerosis (RR-MS) with COPAXONE® in combination with alphacalcidol, with treatment with COPAXONE® in combination with placebo. The clinical objective is to evaluate the effect of treatments on MRI variables, clinical evaluations and immunological profile.

The design of this trial is a randomized, double-masked, 2-arm study of COPAXONE® in combination with alphacalcidol versus COPAXONE® in combination with placebo for the treatment of relapsing-remitting multiple sclerosis. Twenty patients with RR-MS who meet the inclusion/exclusion criteria are enrolled per arm. Patients are randomized and receive either 20 mg SQ (subcutaneous) of COPAXONE® daily plus an oral dose of placebo daily or 20 mg SQ of COPAXONE® in combination with 50 mg alphacalcidol every 12 hours.

Participant inclusion criteria are as follows: 1) men or women age 18 to 50 years; 2) RR-MS according to the guidelines from the International Panel on the Diagnosis of MS (McDonald et al.); 3) two separate documented relapses in the last two years; 4) active MRI with at least one gadolinium(Gd)-enhancing lesion in the MRI scan at screening; 5) EDSS (extended disability status scale) score between 1.0 and 5.0; 6) no relapse during screening period; 6) pre-treatment with COPAXONE® for at least three weeks, but no more than four weeks, prior to baseline visit; and 7) ability to understand and provide informed consent.

Participant exclusion criteria include the following: 1) normal brain MRI; 2) prior treatment with COPAXONE® other than the scheduled three to four week pretreatment prior to baseline

visit; 3) previous treatment with immunomodulating agents such as interferon beta or IVIg for the last 6 months prior to entry; 4) previous use of immunosuppressive agents (including azathioprine) in the last 12 months prior study entry; 5) steroid treatment one month prior to entry; 6) women not willing to practice reliable methods of contraception; 7) pregnant or nursing women; 8) life threatening or clinically significant diseases; 9) history of alcohol and drug abuse within 6 months prior enrollment; 10) known history of sensitivity to Gd; 11) uncontrolled and uncontrollable head movements (tremor, tics, etc.), muscle spasms, significant urinary urgency and claustrophobia, which will prevent the subject from lying still during the MRI scan; and 12) participation in other investigational therapy in the last 90 days.

MRI scans are performed during the screening visit (for eligibility) and at months 5, 10, 11 and 12. Full physical and neurological examinations are performed at screening, baseline and at months 2, 5, 9 and 12. Safety laboratory is performed at screening baseline and at months 1, 2, 5, 9 and 12. In addition, blood Ca^{+} levels are monitored on the first and second months after baseline visit. The immunological profile is monitored at baseline and at months 1, 2, 4, and 5.

Primary efficacy endpoints include the following: 1) MRI variables as measured on months 10, 11, and 12; 2) total number and volume of T1 GD-enhanced lesions; 3) total number of new T2 lesions; and 4) total volume of T2 lesions. Secondary efficacy endpoints encompass the following: 1) changes in immunological parameters; and 2) PBMC proliferation in response to GA in vitro. The tertiary efficacy endpoints are as follows: 1) change from baseline in relapse rate and MS Functional Composite Score (MSFC); and 2) brain atrophy. Tolerability is evaluated with reference to the following: 1) percentage of subjects who discontinue the study; and 2) percentage of subjects who

discontinue the study due to adverse events. Safety is evaluated with reference to 1) adverse event frequency and severity; 2) changes in vital signs and 3) clinical laboratory values.

Patients treated with the COPAXONE® and alphacalcidol combination exhibit a comparable or greater reduction in T1 and T2 Gd-enhancing lesions and other lesions, as compared to the group receiving COPAXONE® and placebo. Additionally, the group receiving the COPAXONE® and alphacalcidol combination demonstrate a comparable or greater reduction in the number of relapses per year as compared with the group receiving COPAXONE® and placebo.

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What is claimed:

1. A method of treating a subject afflicted with a form of multiple sclerosis comprising periodically administering to the subject an amount of glatiramer acetate and an amount of alphacalcidol, wherein the amounts when taken together are effective to alleviate a symptom of the form of multiple sclerosis in the subject so as to thereby treat the subject.

2. The method of claim 1, wherein the form of multiple sclerosis is relapsing-remitting multiple sclerosis.

3. The method of claim 1, wherein the subject is a human being.

4. The method of claim 1, wherein each of the amount of glatiramer acetate when taken alone, and the amount of alphacalcidol when taken alone is effective to alleviate the symptom of the form of multiple sclerosis.

5. The method of claim 1, wherein either the amount of glatiramer acetate when taken alone, the amount of alphacalcidol when taken alone or each such amount when taken alone is not effective to alleviate the symptom of the form of multiple sclerosis.

6. The method of claim 1, wherein the symptom is the frequency of relapses, the frequency of clinical exacerbation, or the accumulation of physical disability.

7. The method of claim 1, wherein the amount of glatiramer acetate is in the range from 10 to 600 mg/week.

8. The method of claim 7, wherein the amount of glatiramer acetate is 300 mg/week.

9. The method of claim 1, wherein the amount of glatiramer acetate is in the range from 50 to 150 mg/day.

10. The method of claim 9, wherein the amount of glatiramer acetate is 100 mg/day.

11. The method of claim 1, wherein the amount of glatiramer acetate is in the range from 10 to 80 mg/day.

12. The method of claim 11, wherein the amount of glatiramer acetate is 20 mg/day.

13. The method of claim 1, wherein the periodic administration of glatiramer acetate is effected daily.

14. The method of claim 1, wherein the periodic administration of glatiramer acetate is effected twice daily at one half the amount.

15. The method of claim 1, wherein the periodic administration of glatiramer acetate is effected once every 5 to 9 days.

16. The method of claim 1, wherein the administration of the glatiramer acetate substantially precedes the administration of the alphacalcidol.

17. The method of claim 1, wherein the administration of the alphacalcidol substantially precedes the administration of the glatiramer acetate.

18. The method of claim 1, wherein the administration of the glatiramer acetate is effected subcutaneously, intraperitoneally, intravenously, intramuscularly, intraocularly or orally and the administration of the alphacalcidol is effected orally.

19. The method of claim 18, wherein the administration of the glatiramer acetate is effected subcutaneously and the administration of the alphacalcidol is effected orally.

20. A package comprising

i) a first pharmaceutical composition comprising an amount of glatiramer acetate and a pharmaceutically acceptable carrier;

ii) a second pharmaceutical composition comprising an amount of alphacalcidol and a pharmaceutically acceptable carrier; and

iii) instructions for use of the first and second pharmaceutical compositions together to alleviate a symptom of a form of multiple sclerosis in a subject.

21. The package of claim 20, wherein the amount of glatiramer acetate is 300 mg.

22. The package of claim 20, wherein the amount of glatiramer acetate is 20 mg.

23. A pharmaceutical composition comprising an amount of glatiramer acetate and an amount of alphacalcidol, wherein the amounts when taken together are effective to alleviate a symptom of a form of multiple sclerosis in a subject.

24. The pharmaceutical composition of claim 23, wherein each of the amount of glatiramer acetate when taken alone and the amount of alphacalcidol when taken alone is effective to alleviate the symptom of multiple sclerosis.

25. The pharmaceutical composition of claim 23, wherein either of the amount of glatiramer acetate when taken alone, or the amount of alphacalcidol when taken alone or each such amount when taken alone is not effective to alleviate the symptom of

multiple sclerosis.

26. A product containing glatiramer acetate and alphacalcidol as a combined preparation for simultaneous, separate or sequential use in treating a form of multiple sclerosis.

27. A product containing glatiramer acetate and alphacalcidol as a combined preparation for simultaneous, separate or sequential use in alleviating a symptom of a form of multiple sclerosis.

32. Use of alphacalcidol for the manufacture of a medicament for use in alleviating a symptom of a form of multiple sclerosis in a patient who is already being treated with glatiramer acetate.

AMENDED CLAIMS UNDER Art 19

[received by the international Bureau on 30 August 2004 (30.08.04),
The claims are renumbered, total sheets 4.

What is claimed:

1. A method of treating a subject afflicted with a form of multiple sclerosis comprising periodically administering to the subject an amount of glatiramer acetate and an amount of alphacalcidol, wherein the amounts when taken together are effective to alleviate a symptom of the form of multiple sclerosis in the subject so as to thereby treat the subject.

2. The method of claim 1, wherein the form of multiple sclerosis is relapsing-remitting multiple sclerosis.

3. The method of claim 1, wherein the subject is a human being.

4. The method of claim 1, wherein each of the amount of glatiramer acetate when taken alone, and the amount of alphacalcidol when taken alone is effective to alleviate the symptom of the form of multiple sclerosis.

5. The method of claim 1, wherein either the amount of glatiramer acetate when taken alone, the amount of alphacalcidol when taken alone or each such amount when taken alone is not effective to alleviate the symptom of the form of multiple sclerosis.

6. The method of claim 1, wherein the symptom is the frequency of relapses, the frequency of clinical exacerbation, or the accumulation of physical disability.

7. The method of claim 1, wherein the amount of glatiramer acetate is in the range from 10 to 600 mg/week.

8. The method of claim 7, wherein the amount of glatiramer acetate is 300 mg/week.

9. The method of claim 1, wherein the amount of glatiramer acetate is in the range from 50 to 150 mg/day.

10. The method of claim 9, wherein the amount of glatiramer acetate is 100 mg/day.

11. The method of claim 1, wherein the amount of glatiramer acetate is in the range from 10 to 80 mg/day.

12. The method of claim 11, wherein the amount of glatiramer acetate is 20 mg/day.

13. The method of claim 1, wherein the periodic administration of glatiramer acetate is effected daily.

14. The method of claim 1, wherein the periodic administration of glatiramer acetate is effected twice daily at one half the amount.

15. The method of claim 1, wherein the periodic administration of glatiramer acetate is effected once every 5 to 9 days.

16. The method of claim 1, wherein the administration of the glatiramer acetate substantially precedes the administration of the alphacalcidol.

17. The method of claim 1, wherein the administration of the alphacalcidol substantially precedes the administration of the glatiramer acetate.

18. The method of claim 1, wherein the administration of the glatiramer acetate is effected subcutaneously, intraperitoneally, intravenously, intramuscularly, intraocularly or orally and the administration of the alphacalcidol is effected orally.

19. The method of claim 18, wherein the administration of the glatiramer acetate is effected subcutaneously and the administration of the alphacalcidol is effected orally.

20. A package comprising

i) a first pharmaceutical composition comprising an amount of glatiramer acetate and a pharmaceutically acceptable carrier;

ii) a second pharmaceutical composition comprising an amount of alphacalcidol and a pharmaceutically acceptable carrier; and

iii) instructions for use of the first and second pharmaceutical compositions together to alleviate a symptom of a form of multiple sclerosis in a subject.

21. The package of claim 20, wherein the amount of glatiramer acetate is 300 mg.

22. The package of claim 20, wherein the amount of glatiramer acetate is 20 mg.

23. A pharmaceutical composition comprising an amount of glatiramer acetate and an amount of alphacalcidol, wherein the amounts when taken together are effective to alleviate a symptom of a form of multiple sclerosis in a subject.

24. The pharmaceutical composition of claim 23, wherein each of the amount of glatiramer acetate when taken alone and the amount of alphacalcidol when taken alone is effective to alleviate the symptom of multiple sclerosis.

25. The pharmaceutical composition of claim 23, wherein either of the amount of glatiramer acetate when taken alone, or the amount of alphacalcidol when taken alone or each such amount when taken alone is not effective to alleviate the symptom of multiple sclerosis.

26. A product containing glatiramer acetate and alphacalcidol as a combined preparation for simultaneous, separate or sequential use in treating a form of multiple sclerosis.

27. A product containing glatiramer acetate and alphacalcidol as a combined preparation for simultaneous, separate or sequential use in alleviating a symptom of a form of multiple sclerosis.

28. Use of alphacalcidol for the manufacture of a medicament for use in alleviating a symptom of a form of multiple sclerosis in a patient who is already being treated with glatiramer acetate.

29. Use of alphacalcidol for the manufacture of a medicament for use in alleviating a symptom of a form of multiple sclerosis in a patient population that is being treated with glatiramer acetate.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US04/06799

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 9/00, 38/16, 31/05, 31/045
US CL : 424/400; 514/18, 732, 738

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 424/400; 514/18, 732, 738

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST, STN

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6,214,791 B1 (ARNON et al.) 10 April 2001 (10.04.2001), see entire document.	1-27 and 32
Y	US 5,716,946 A (DELUCA et al.) 10 February 1998 (10.02.1998), see entire document.	1-27 and 32
Y	US 2002/0028830 A1 (DELUCA et al.) 07 March 2002 (07.03.2002), see paragraph [0010].	1-27 and 32

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 July 2004 (27.07.2004)	30 AUG 2004
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703) 305-3230	Authorized officer Christopher R. Tate Telephone No. 571-272-1600

Form PCT/ISA/210 (second sheet) (July 1998)