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(54) Title: METHOD OF TREATING MULTIPLE SCLEROSIS

(57) Abstract: This invention provides a method of alleviating a symptom of a patient suffering from a relapsing form of multiple sclerosis which comprises periodically administering to the patient by subcutaneous injection a single dose of a pharmaceutical composition comprising 40 mg of glatiramer acetate so as to thereby alleviate the symptom of the patient. This invention also provides a method of reducing Gd-enhancing lesions in the brain and a pharmaceutical composition in a unit dosage.

METHOD OF TREATING MULTIPLE SCLEROSIS

Throughout this application various publications are referenced by their full citations. 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.

Background Of The Invention

One of the more common chronic neurologic diseases in human adults is multiple sclerosis ("MS"). MS is a chronic, inflammatory CNS disease characterized pathologically by demyelination. MS has also been classified as an autoimmune disease. MS disease activity can be monitored by magnetic resonance imaging (MRI) of the brain, accumulation of disability, as well as rate and severity of relapses.

There are five main forms of multiple sclerosis: 1) benign multiple sclerosis; 2) relapsing-remitting multiple sclerosis (RRMS); 3) secondary progressive multiple sclerosis (SPMS); 4) primary progressive multiple sclerosis (PPMS); and 5) progressive-relapsing multiple sclerosis (PRMS) (What are the Types of Multiple Sclerosis?, 2005 <http://imaginis.com/multiple-sclerosis/types-of-ms.asp? mode=1>). Chronic progressive multiple sclerosis is a term used to collectively refer to SPMS, PPMS, and PRMS (Types of Multiple Sclerosis (MS), 2005 <http://www.themcfox.com/multiple-sclerosis/types-of-ms/ types-of-multiple-sclerosis.htm>). The relapsing

forms of multiple sclerosis are SPMS with superimposed relapses, RRMS and PRMS.

Benign multiple sclerosis is a retrospective diagnosis which 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 RRMS 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 RRMS. SPMS may evolve from RRMS. Patients afflicted with SPMS have relapses, a diminishing degree of recovery during remissions, less frequent remissions and more pronounced neurological deficits than RRMS patients. Enlarged ventricles, which are markers for atrophy of the corpus callosum, midline center and spinal cord, are visible on MRI of patients with SPMS. PPMS 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 PPMS. PRMS 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 PRMS (Multiple sclerosis: its diagnosis, symptoms, types and stages, 2003 <http://www.albany.net/~tjc/multiple-sclerosis.html>).

Glatiramer acetate (GA), a mixture of polypeptides which do not all have the same amino acid sequence, is marketed under the tradename Copaxone®. GA comprises the acetate

salts of polypeptides containing L-glutamic acid, L-alanine, L-tyrosine and L-lysine at average molar fractions of 0.141, 0.427, 0.095 and 0.338, respectively. The average molecular weight of Copaxone® is between 5,000 and 9,000 daltons. ("Copaxone", Physician's Desk Reference, (2005), Medical Economics Co., Inc., (Montvale, NJ), 3115.) Chemically, glatiramer acetate is designated L-glutamic acid polymer with L-alanine, L-lysine, L-tyrosine, acetate (salt). Its structural formula is:

$$(Glu, Ala, Lys, Tyr)_x \cdot \chi CH_3COOH$$
$$(C_5H_9NO_4 \cdot C_3H_7NO_2 \cdot C_6H_{14}N_2O_2 \cdot C_9H_{11}NO_3)_x \cdot \chi C_2H_4O_2$$
CAS - 147245-92-9

("Copaxone", Physician's Desk Reference, (2000), Medical Economics Co., Inc., (Montvale, NJ), 3115.) Copaxone® (20 mg glatiramer acetate injection) is an approved therapy for patients with relapsing remitting multiple sclerosis (RRMS).

Glatiramer acetate has also been disclosed for use in the treatment of other autoimmune diseases (U.S. Patent Publication No. 2002/0055466 A1 (R. Aharoni et al.), inflammatory non-autoimmune diseases (U.S. Patent Publication No. 2005/0014694 A1 (V. Wee Yong et al.); and U.S. Patent Application No. 2002/0077278 A1, published June 20, 2002 (Young et al.)) and other diseases (U.S. Patent Publication Nos. 2003/0004099 A1 and 2002/0037848 A1 (Eisenbach-Schwartz, et al.); U.S. Patent No. 6,514,938 B1, issued February 4, 2003 (Gad et al.); PCT International Publication No. WO 01/60392, published August 23, 2001 (Gilbert et al.); PCT International Publication No. WO 00/27417, published May 19, 2000

(Aharoni et al.); and PCT International Publication No. WO 01/97846, published December 27, 2001 (Moses et al.)).

The 20mg/day subcutaneous dose has been shown to reduce the total number of enhancing lesions in MS patients as measured by MRI (G. Comi et al., European/Canadian Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of the Effects of Glatiramer Acetere on Magnetic Resonance Imaging-Measured Disease Activity and Burden in Patients with Relapsing Multiple Sclerosis, Ann. Neurol. 49:290-297 (2001)). However, disclosed herein is the finding that administration of glatiramer acetate at a dose of 40 mg/day significantly improves efficacy but does not have a corresponding increase in adverse reactions experienced by the patient.

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