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(54) Title: COMBINATION THERAPY USING MEMANTINE AND GLITAZONES

(57) Abstract: The present invention relates to combinations comprising memantine and a glitazone and the use of such combinations in the treatment of neurodegenerative disorders and/or to provide neuroprotection.



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## COMBINATION THERAPY USING MEMANTINE AND GLITAZONES

### FIELD OF THE INVENTION

[0001] The present invention relates to combinations comprising memantine and a glitazone and the use of such combinations in the treatment of neurodegenerative diseases and/or to provide neuroprotection.

### BACKGROUND OF THE INVENTION

[0002] NMDA receptor antagonists potentially have a wide range of therapeutic applications in numerous CNS disorders such as acute neurodegeneration (e.g., associated with stroke and trauma), chronic neurodegeneration (e.g., associated with Parkinson's disease, Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS)), epilepsy, drug dependence, depression, anxiety, and chronic pain (for reviews see: Parsons *et al.*, *Drug News Perspect.*, 1998, 11:523-533; Parsons *et al.*, 1999, *supra*; Jentsch and Roth, *Neuropsychopharmacology*, 1999, 20: 201-205; Doble, *Therapie*, 1995, 50: 319-337). Functional inhibition of NMDA receptors can be achieved through actions at different recognition sites within the NMDA receptor complex, such as: the primary transmitter site (competitive), the phencyclidine site located inside the cation channel (uncompetitive), the polyamine modulatory site and the strychnine-insensitive, co-agonistic, allosteric, glycine site (glycine B) (Parsons *et al.*, 1999, *supra*).

[0003] It is believed that the excitatory neurotransmitter glutamate plays an important role in the pathophysiology (as opposed to etiology) of neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. About 70% of all excitatory synapses in the CNS are stimulated by glutamate, and dysfunctional, chronic release of glutamate can produce a prolonged excitatory effect via glutamate receptor activation. This prolonged activation is

mediated by the NMDA glutamate receptor and can result in the degeneration and death of cortical neurons.

[0004] Memantine (1-amino-3,5-dimethyl adamantane, disclosed, e.g., in U.S. Patents No. 4,122,193; 4,273,774; 5,061,703) is a systemically-active uncompetitive NMDA receptor antagonist having moderate affinity for the receptor and strong voltage dependency and rapid blocking/unblocking kinetics. Memantine has been shown to be useful in alleviation of various progressive neurodegenerative disorders such as dementia in patients with moderate to severe Alzheimer's disease, Parkinson's disease, and spasticity (see, e.g., U. S. Patents No. 5,061,703; 5,614,560, and 6,034,134; Parsons *et al.*, 1999, *supra*; Möbius, ADAD, 1999,13:S172-178; Danysz *et al.*, Neurotox. Res., 2000, 2:85-97; Winblad and Poritis, Int. J. Geriatr. Psychiatry, 1999, 14:135-146; Görtelmeyer *et al.*, 1992, *supra*; Danysz *et al.*, Curr. Pharm. Des., 2002, 8:835-843; Jirgensons *et. al.*, Eur. J. Med. Chem., 2000, 35: 555-565). Memantine, has also been suggested to be useful in the treatment of AIDS dementia (U.S. Patent No. 5,506,231), neuropathic pain (U.S. Patent No. 5,334,618), cerebral ischemia (U.S. Patent No. 5,061,703), epilepsy, glaucoma, hepatic encephalopathy, multiple sclerosis, stroke, and tardive dyskinesia (Parsons *et al.*, 1999, *supra*). Memantine is currently approved in Europe and the United States for the treatment of Alzheimer's disease.

[0005] It has been reported that peroxisome proliferator-activated receptor- $\gamma$  (PPAR $\gamma$ ) agonists, such as the thiazolidinedione class of anti-diabetic agents (i.e., glitazones), may be useful in the treatment of Alzheimer's disease. Glitazones have been shown to ameliorate microglial reactivity, and it has been suggested that this activity may be associated with activation of PPAR $\gamma$ , which, in turn, inhibits inflammatory responses in the brain and negatively modulates amyloidogenesis (Landreth, *Experimental Neurology*, 2006, 199, 245-248).

[0006] It has also been reported that rosiglitazone therapy improves cognition in some Alzheimer's patients (Watson, et al., *Am. J. Geriatr. Psychiatry*, **2005**, *13*, 950-958; Risner, et al., *Pharmacogenomics Journal*, **2006**, *6*, 246-254). Moreover, rosiglitazone (Pedersen, et al., *Exp. Neurology*, **2006**, *199*, 265-273) and pioglitazone (Heneka, et al., *Brain*, **2005**, *128*, 1442-1453) exhibit beneficial therapeutic effects in a mouse model for Alzheimer's disease. Pioglitazone and rosiglitazone also exhibit protective effects in a rat model of mild forebrain ischemia reperfusion injury. (Collino, et al., *Eur. J. Pharmacol.*, **2006**, *530*, 70-80).

[0007] PPAR $\gamma$  agonists have also exhibited activity in animal models of stroke, Parkinson's disease, multiple sclerosis, and amyotrophic lateral sclerosis, which activity may be attributable to the anti-inflammatory actions associated with PPAR $\gamma$  agonists (Landreth, *Experimental Neurology*, **2006**, *199*, 245-248).

[0008] In addition to exhibiting activity as PPAR $\gamma$  agonists, it has also been reported that the thiazolidinedione class of anti-diabetic agents influence mitochondrial function (Feinstein, et al., *Biochem. Pharmacol.*, **2005**, *70*, 177-188; Roses, et al., *Pharmacogenomics Journal*, **2007**, *7*, 10-28). Mitochondrial dysfunction has been implicated in the pathogenesis of a number of neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, progressive supranuclear palsy, schizophrenia, motor neuron diseases (e.g., amyotrophic lateral sclerosis), and Huntington's disease (Roses, et al., *supra*).

[0009] Pioglitazone has been shown to bind to MitoNEET (Colca, et al., *Am. J. Physiol. Endocrinol. Metab.*, **2004**, E252-E260) a protein located within the mitochondrial membrane, which protein has been recently characterized (Paddock, et al., *PNAS*, **2007**, *104*, 14342-14347). Pioglitazone has been shown to induce mitochondrial biogenesis and to reduce mitochondrial oxidative stress in a neuron-like cell line (Ghosh, et al., *Mol. Pharmacol.*, **2007**, *71*, 1695-1702), and rosiglitazone

has also been shown to stimulate mitochondrial biogenesis in mouse brain (Roses, et al., *supra*).

### **SUMMARY OF THE INVENTION**

[0010] The present invention relates to combinations comprising memantine and a glitazone and the use of such combinations in the treatment of neurodegenerative diseases and/or to provide neuroprotection.

[0011] A further aspect of the invention relates to combinations comprising memantine and a glitazone and the use of such combinations in the treatment of neurodegenerative diseases, including Alzheimer's disease, stroke, multiple sclerosis, progressive supranuclear palsy, schizophrenia, Huntington's disease, and amyotrophic lateral sclerosis, and/or to provide neuroprotection.

[0012] A further aspect of the invention relates to combinations comprising memantine and a glitazone selected from pioglitazone, troglitazone, rosiglitazone, ciglitazone, englitazone, darglitazone, rivoglitazone, isaglitazone, KRP 297, T 174, and NP 0110, and the use of such combinations in the treatment of neurodegenerative diseases, including Alzheimer's disease, stroke, multiple sclerosis, progressive supranuclear palsy, schizophrenia, Huntington's disease, and amyotrophic lateral sclerosis, and/or to provide neuroprotection.

[0013] A further aspect of the invention relates to combinations comprising memantine and a glitazone selected from pioglitazone, troglitazone, rosiglitazone, ciglitazone, englitazone, darglitazone, rivoglitazone, isaglitazone, KRP 297, T 174, and NP 0110, and the use of such combinations in the treatment of Alzheimer's disease.

[0014] A further aspect of the invention relates to combinations comprising memantine and pioglitazone as well as a method of treating an individual diagnosed

with Alzheimer's disease, comprising administering to the individual an effective amount of a combination of memantine and pioglitazone.

[0015] A further aspect of the invention relates to the use of a combination comprising memantine and a glitazone for the manufacture of a medicament for the treatment of neurodegenerative diseases and/or to provide neuroprotection.

[0016] A further aspect of the invention relates to the use of a combination comprising memantine and a glitazone for the manufacture of a medicament for the treatment of Alzheimer's disease, stroke, multiple sclerosis, and amyotrophic lateral sclerosis.

[0017] A further aspect of the invention relates to the use of a combination comprising memantine and a glitazone selected from pioglitazone, troglitazone, rosiglitazone, ciglitazone, englitazone, darglitazone, rivoglitazone, isaglitazone, KRP 297, T 174, and NP 0110, for the manufacture of a medicament for the treatment of neurodegenerative diseases, including Alzheimer's disease, stroke, multiple sclerosis, and amyotrophic lateral sclerosis.

[0018] A further aspect of the invention relates to the use of a combination comprising memantine and a glitazone selected from pioglitazone, troglitazone, rosiglitazone, ciglitazone, englitazone, darglitazone, rivoglitazone, isaglitazone, KRP 297, T 174, and NP 0110, for the manufacture of a medicament for the treatment of Alzheimer's disease.

[0019] A further aspect of the invention relates to the use of a combination comprising memantine and pioglitazone for the manufacture of a medicament for treatment of an individual diagnosed with Alzheimer's disease.

[0020] An additional aspect of the invention relates to a pharmaceutical composition for the treatment of neurodegenerative diseases and/or to provide neuroprotection

comprising a therapeutically effective amount of a combination of memantine and a glitazone, and at least one pharmaceutically acceptable excipient.

[0021] A further aspect of the invention relates to a pharmaceutical composition for the treatment of neurodegenerative diseases, including Alzheimer's disease, stroke, multiple sclerosis, progressive supranuclear palsy, schizophrenia, Huntington's disease, and amyotrophic lateral sclerosis, and/or to provide neuroprotection, comprising a therapeutically effective amount of a combination of memantine and a glitazone, including pioglitazone, troglitazone, rosiglitazone, ciglitazone, englitazone, darglitazone, rivoglitazone, isaglitazone, KRP 297, T 174, and NP 0110, and at least one pharmaceutically acceptable excipient.

[0022] A further aspect of the invention relates to a pharmaceutical composition for the treatment of Alzheimer's disease comprising a therapeutically effective amount of a combination comprising memantine and pioglitazone, and at least one pharmaceutically acceptable carrier or excipient.

[0023] A further aspect of the invention relates to a pharmaceutical composition for the treatment of Alzheimer's disease comprising a therapeutically effective amount of a combination comprising memantine and pioglitazone in an immediate or modified release formulation.

#### **DETAILED DESCRIPTION OF THE INVENTION**

[0024] The term "combination" applied to active ingredients is used herein to define a single pharmaceutical composition (formulation) comprising two active agents (e.g., a pharmaceutical composition comprising memantine and pioglitazone) or two separate pharmaceutical compositions, each comprising an active agent (e.g. a pharmaceutical composition comprising memantine or pioglitazone), to be administered conjointly.

[0025] Within the meaning of the present invention, the term "conjoint administration" is used to refer to administration of memantine and a glitazone compound (for example, pioglitazone) simultaneously in one composition, or simultaneously in different compositions, or sequentially. For the sequential administration to be considered "conjoint", however, memantine and the second active agent must be administered separated by a time interval which still permits the resultant beneficial effect for treating a neurodegenerative disease (such as Alzheimer's disease) in a mammal.

[0026] As used herein, the term neurodegenerative diseases includes Alzheimer's disease, stroke, multiple sclerosis, progressive supranuclear palsy, schizophrenia, Huntington's disease, and amyotrophic lateral sclerosis.

[0027] Memantine (1-amino-3,5-dimethyl adamantane) is disclosed in U.S. Patent Nos. 4,122,193; 4,273,774; 5,061,703, the subject matter of which is hereby incorporated by reference. Memantine, may be used according to the invention in the form of any of its pharmaceutically acceptable salts (e.g., memantine hydrochloride), solvates, isomers, conjugates, prodrugs, metabolites, and derivatives, any references to memantine in this description should be understood as also referring to such salts, solvates, isomers, conjugates, prodrugs, metabolites, and derivatives.

[0028] As used herein, the term glitazone refers to the thiazolinedione class of anti-diabetic agents. Examples of glitazones include pioglitazone, troglitazone, rosiglitazone, ciglitazone, englitazone, darglitazone, rivoglitazone, isaglitazone, KRP 297, T 174, and NP 0110.

[0029] Pioglitazone (5-((4-(2-(5-ethyl-pyridin-2-yl)-ethoxy)-benzyl)-thiazolidine-2,4-dione) is disclosed in U.S. Patent No. 4,687,777, the subject matter of which is



hereby incorporated by reference. Pioglitazone may be used according to the invention in the form of any of its pharmaceutically acceptable salts (e.g., pioglitazone hydrochloride), solvates, isomers, conjugates, prodrugs, metabolites, and derivatives, any references to pioglitazone in this description should be understood as also referring to such salts, solvates, isomers, conjugates, prodrugs, metabolites, and derivatives.

[0030] Troglitazone (5-(4-(6-Hydroxy-2,5,7,8-tetramethyl-chroman-2-yl-methoxy)-benzyl)-thiazolidine-2,4-dione) is disclosed in US Patent No. 4,572,912, the subject matter of which is hereby incorporated by reference. Troglitazone may be used according to the invention in the form of any of its pharmaceutically acceptable salts, solvates, isomers, conjugates, prodrugs, metabolites, and derivatives, any references to troglitazone in this description should be understood as also referring to such salts, solvates, isomers, conjugates, prodrugs, metabolites, and derivatives.

[0031] Rosiglitazone (5-(4-(2-(Methyl-pyridin-2-yl-amino)-ethoxy)-benzyl)-thiazolidine-2,4-dione) is disclosed in U.S. Patent Nos. 5,002,953 and 5,741,803, the subject matter of which is hereby incorporated by reference. Rosiglitazone may be used according to the invention in the form of any of its pharmaceutically acceptable salts (e.g., rosiglitazone maleate), solvates, isomers, conjugates, prodrugs, metabolites, and derivatives, any references to rosiglitazone in this description should be understood as also referring to such salts, solvates, isomers, conjugates, prodrugs, metabolites, and derivatives.

[0032] Ciglitazone (5-(4-(1-Methyl-cyclohexylmethoxy)-benzyl)-thiazolidine-2,4-dione) is disclosed in US Patent No. 4,287,200, the subject matter of which is hereby incorporated by reference. Ciglitazone may be used according to the invention in the form of any of its pharmaceutically acceptable salts, solvates, isomers, conjugates, prodrugs, metabolites, and derivatives, any references to ciglitazone in this

description should be understood as also referring to such salts, solvates, isomers, conjugates, prodrugs, metabolites, and derivatives.

[0033] Englitazone (5-((2-benzyl-3,4-dihydro-2H-1-benzopyran-6-yl)-methyl)-thiazolidine-2,4-dione) is disclosed in Clark, et al. (*J. Med. Chem.*, **1991**, 34, 319-325). Englitazone may be used according to the invention in the form of any of its pharmaceutically acceptable salts (e.g. englitazone sodium salt), solvates, isomers, conjugates, prodrugs, metabolites, and derivatives, any references to englitazone in this description should be understood as also referring to such salts, solvates, isomers, conjugates, prodrugs, metabolites, and derivatives.

[0034] Darglitazone (5-(4-(3-(5-methyl-2-phenyl-4-oxazolyl)propionyl)-benzyl)thiazolidine-2,4-dione) is disclosed in Hulin, et al. (*J. Med. Chem.*, **1992**, 35, 1853-1864) Darglitazone may be used according to the invention in the form of any of its pharmaceutically acceptable salts, solvates, isomers, conjugates, prodrugs, metabolites, and derivatives, any references to darglitazone in this description should be understood as also referring to such salts, solvates, isomers, conjugates, prodrugs, metabolites, and derivatives.

[0035] Rivoglitazone (5-(4-(6-methoxy-1-methyl-1H-benzimidazol-2-ylmethoxy)benzyl)thiazolidin-2,4-dione) is disclosed in US Patent Nos. 5,886,014 and 6,706,746 the subject matter of which is hereby incorporated by reference. Rivoglitazone may be used according to the invention in the form of any of its pharmaceutically acceptable salts (e.g. rivoglitazone hydrochloride), solvates, isomers, conjugates, prodrugs, metabolites, and derivatives, any references to rivoglitazone in this description should be understood as also referring to such salts, solvates, isomers, conjugates, prodrugs, metabolites, and derivatives.

[0036] Isaglitazone (5-(6-(2-fluorobenzyloxy)-2-naphthyl)-methyl-thiazolidine-2,4-dione) is disclosed in US Patent No. 5,594,016, the subject matter of which is hereby

incorporated by reference. Isaglitazone may be used according to the invention in the form of any of its pharmaceutically acceptable salts (e.g., isaglitazone sodium salt), solvates, isomers, conjugates, prodrugs, metabolites, and derivatives, any references to isaglitazone in this description should be understood as also referring to such salts, solvates, isomers, conjugates, prodrugs, metabolites, and derivatives.

[0037] KRP 297 (N-(4-Trifluoromethylbenzyl)-5-(2,4-dioxothiazolidin-5-yl)methyl-2-hydroxybenzamide) is disclosed in US Patent No. 6,001,862, the subject matter of which is hereby incorporated by reference. KRP 297 may be used according to the invention in the form of any of its pharmaceutically acceptable salts, solvates, isomers, conjugates, prodrugs, metabolites, and derivatives, any references to KRP 297 in this description should be understood as also referring to such salts, solvates, isomers, conjugates, prodrugs, metabolites, and derivatives.

[0038] T 174 (5-((2-(2-naphthyl)-benzoxazol-5-yl)-methyl)thiazolidine-2,4-dione) is disclosed in US Patent No. 4,897,393, the the subject matter of which is hereby incorporated by reference. T 174 may be used according to the invention in the form of any of its pharmaceutically acceptable salts, solvates, isomers, conjugates, prodrugs, metabolites, and derivatives, any references to T 174 in this description should be understood as also referring to such salts, solvates, isomers, conjugates, prodrugs, metabolites, and derivatives.

[0039] NP 0110 (5-((7-(4-trifluoromethylbenzyloxy)-3-quinolyl)-methyl)thiazolidine-2,4-dione) is disclosed in US Patent No. 5,693,651, the the subject matter of which is hereby incorporated by reference. NP 0110 may be used according to the invention in the form of any of its pharmaceutically acceptable salts, solvates, isomers, conjugates, prodrugs, metabolites, and derivatives, any references to NP 0110 in this description should be understood as also referring to such salts, solvates, isomers, conjugates, prodrugs, metabolites, and derivatives.

[0040] Pharmaceutically acceptable salts include, but are not limited to, acid addition salts, such as those made with hydrochloric, methanesulfonic, hydrobromic, hydroiodic, perchloric, sulfuric, nitric, phosphoric, acetic, propionic, glycolic, lactic, pyruvic, malonic, succinic, fumaric, tartaric, citric, benzoic, carbonic, cinnamic, mandelic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, benzenesulfonic, p-toluene sulfonic, cyclohexanesulfamic, salicylic, p-aminosalicylic, 2-phenoxybenzoic, and 2-acetoxybenzoic acid. All of these salts (or other similar salts) may be prepared by conventional means. The nature of the salt is not critical, provided that it is non-toxic and does not substantially interfere with the desired pharmacological activity.

[0041] The term "analog" or "derivative" is used herein in the conventional pharmaceutical sense, to refer to a molecule that structurally resembles a reference molecule (such as memantine), but has been modified in a targeted and controlled manner to replace one or more specific substituents of the referent molecule with an alternate substituent, thereby generating a molecule which is structurally similar to the reference molecule. Synthesis and screening of analogs (e.g., using structural and/or biochemical analysis), to identify slightly modified versions of a known compound which may have improved or biased traits (such as higher potency and/or selectivity at a specific targeted receptor type, greater ability to penetrate mammalian blood-brain barriers, fewer side effects, etc.) is a drug design approach that is well known in pharmaceutical chemistry.

[0042] The term "treat" is used herein to mean to relieve or alleviate at least one symptom of a disease in a subject. Within the meaning of the present invention, the term "treat" also denotes to arrest, delay the onset (*i.e.*, the period prior to clinical manifestation of a disease) and/or reduce the risk of developing or worsening a disease.

[0043] The term "therapeutically effective" applied to dose or amount refers to that quantity of a compound or pharmaceutical composition that is sufficient to result in a desired activity upon administration to a mammal in need thereof.

[0044] The term "sub-threshold" refers to the amount of an active ingredient inadequate to produce a response, *i.e.*, an amount below the minimum effective amount when the active ingredient is used as monotherapy.

[0045] The term "sub-optimal" in the same context means an amount of an active ingredient that produces a response but not to its full extent, which would be achieved with a higher amount.

[0046] The term "additive" refers to the combined effect of administering two compounds, where the overall response is equal to, or nearly equal to the sum of the responses if the compounds were administered as monotherapy.

[0047] The term "synergistic" refers to the combined effect of administering two therapeutic compounds where the overall response is greater than the sum of the two individual effects. The term synergy also refers to the combined effect of administering an amount of one compound that, when administered as monotherapy, produces no measurable response but, when administered in combination with another therapeutic compound, produces an overall response that is greater than that produced by the second compound alone.

[0048] The phrase "pharmaceutically acceptable", as used in connection with compositions of the invention, refers to molecular entities and other ingredients of such compositions that are physiologically tolerable and do not typically produce untoward reactions when administered to a mammal (*e.g.*, human). Preferably, as used herein, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or

other generally recognized pharmacopeia for use in mammals, and more particularly in humans.

[0049] The term "carrier" applied to pharmaceutical compositions of the invention refers to a diluent, excipient, or vehicle with which an active substance (e.g., memantine and/or pioglitazone) is administered. Such pharmaceutical carriers can be sterile liquids, such as water, saline solutions, aqueous dextrose solutions, aqueous glycerol solutions, and oils, including those of petroleum, animal, vegetable or synthetic origin, such as peanut oil, soybean oil, mineral oil, sesame oil and the like. Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by A.R. Gennaro, 20<sup>th</sup> Edition.

[0050] The term "about" or "approximately" usually means within 20%, alternatively within 10%, including within 5% of a given value or range. Alternatively, especially in biological systems, the term "about" means within about a log (*i.e.*, an order of magnitude), including within a factor of two of a given value.

[0051] In conjunction with the methods of the present invention, also provided are pharmaceutical compositions comprising a therapeutically effective amount of memantine and/or a therapeutically acceptable amount of a glitazone (for example, pioglitazone). The compositions of the invention may further comprise a carrier or excipient (all pharmaceutically acceptable). The compositions may be formulated for once-a-day administration, twice-a-day administration, or three times a day administration.

[0052] The composition or a single active ingredient of the present invention may be used for the manufacture of a medicament for the treatment of one of the mentioned disorders, wherein the medicament is adapted to or appropriately prepared for a specific administration as disclosed herein (e.g., to once-a-day, twice-a-day

administration, or three times a day administration). For this purpose the package leaflet and/or the patient information contains corresponding information.

[0053] According to the present invention, the dosage form of the compositions may be a solid, semisolid, thin film/flash dose, or liquid formulation according to the following.

[0054] The compositions may be administered orally, topically, parenterally, or mucosally (e.g., buccally, by inhalation, or rectally) in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers. The compositions may be administered orally in the form of a capsule, a tablet, or the like, or as a semi-solid, thin film/flash dose, or liquid formulation (see Remington's Pharmaceutical Sciences, 20<sup>th</sup> Edition, by A.R. Gennaro).

[0055] For oral administration in the form of a tablet or capsule, the compositions may be combined with a non-toxic, pharmaceutically acceptable excipients such as binding agents (e.g., pregelatinized maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g., lactose, sucrose, glucose, mannitol, sorbitol and other reducing and non-reducing sugars, microcrystalline cellulose, calcium sulfate, or calcium hydrogen phosphate); lubricants (e.g., magnesium stearate, talc, or silica, steric acid, sodium stearyl fumarate, glyceryl behenate, calcium stearate, and the like); disintegrants (e.g., potato starch or sodium starch glycolate); or wetting agents (e.g., sodium lauryl sulphate), coloring and flavoring agents, gelatin, sweeteners, natural and synthetic gums (such as acacia, tragacanth or alginates), buffer salts, carboxymethylcellulose, polyethyleneglycol, waxes, and the like.

[0056] The tablets may be coated with a concentrated sugar solution which may contain e.g., gum arabic, gelatine, talcum, titanium dioxide, and the like. Alternatively, the tablets can be coated with a polymer that dissolves in a readily volatile organic

solvent or mixture of organic solvents. In specific embodiments, the active substances are formulated in immediate-release (IR) or modified-release (MR) tablets. Immediate release solid dosage forms permit the release of most or all of the active ingredient over a short period of time, such as 60 minutes or less, and make rapid absorption of the drug possible (for example, immediate release formulations of memantine are disclosed in US Published Application No. 2006/0002999, the subject matter of which is hereby incorporated by reference). Modified release solid oral dosage forms permit the sustained release of the active ingredient over an extended period of time in an effort to maintain therapeutically effective plasma levels over similarly extended time intervals and/or to modify other pharmacokinetic properties of the active ingredient (for example, modified release formulations of memantine are disclosed in US Published Application No. 2006/0051416, the subject matter of which is hereby incorporated by reference).

[0057] For the formulation of soft gelatin capsules, the active substances may be admixed with e.g., a vegetable oil or poly-ethylene glycol. Hard gelatin capsules may contain granules of the active substances using either the above mentioned excipients for tablets e.g., lactose, saccharose, sorbitol, mannitol, starches (e.g., potato starch, corn starch or amylopectin), cellulose derivatives or gelatine. Also liquids or semisolids of the drug can be filled into hard gelatine capsules.

[0058] The compositions of the invention can also be introduced in microspheres or microcapsules, e.g., fabricated from polyglycolic acid/lactic acid (PGLA) (see, e.g., U.S. Patents No. 5,814,344; 5,100,669 and 4,849,222; PCT Publications No. WO 95/11010 and WO 93/07861). Biocompatible polymers may be used in achieving controlled release of a drug, include for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxybutyric acid, polyorthoesters, polyacetals, polyhydropyrans, polycyanoacrylates, and cross-linked or amphipathic block copolymers of hydrogels.



[0059] Formulation of the compositions of the invention in a semi-solid or liquid form may also be used. The active ingredient (i.e., memantine and/or, for example, pioglitazone) may constitute between 0.1 and 99% by weight of the formulation, more specifically between 0.5 and 20% by weight for formulations intended for injection and between 0.2 and 50% by weight for formulations suitable for oral administration.

[0060] In one embodiment of the invention, the compositions are administered in modified release formulations. Modified release dosage forms provide a means for improving patient compliance and for ensuring effective and safe therapy by reducing the incidence of adverse drug reactions. Compared to immediate release dosage forms, modified release dosage forms can be used to prolong pharmacologic action after administration, and to reduce variability in the plasma concentration of a drug throughout the dosage interval, thereby eliminating or reducing sharp peaks.

[0061] A modified release form dosage may comprise a core either coated with or containing a drug. The core being is then coated with a release modifying polymer within which the drug is dispersed. The release modifying polymer disintegrates gradually, releasing the drug over time. Thus, the outer-most layer of the composition effectively slows down and thereby regulates the diffusion of the drug across the coating layer when the composition is exposed to an aqueous environment, i.e. the gastrointestinal tract. The net rate of diffusion of the drug is mainly dependent on the ability of the gastric fluid to penetrate the coating layer or matrix and on the solubility of the drug itself.

[0062] In another embodiment of the invention, the compositions are formulated in oral, liquid formulations. Liquid preparations for oral administration can take the form of, for example, solutions, syrups, emulsions or suspensions, or they can be presented as a dry product for reconstitution with water or other suitable vehicle before use. Preparations for oral administration can be suitably formulated to give controlled or postponed release of the active compound. For example, oral liquid

formulations of memantine are described in PCT Application No. PCT/US2004/037026, the subject matter of which is hereby incorporated by reference.

[0063] For oral administration in liquid form, the compositions may be combined with non-toxic, pharmaceutically acceptable inert carriers (e.g., ethanol, glycerol, water), suspending agents (e.g., sorbitol syrup, cellulose derivatives or hydrogenated edible fats), emulsifying agents (e.g., lecithin or acacia), non-aqueous vehicles (e.g., almond oil, oily esters, ethyl alcohol or fractionated vegetable oils), preservatives (e.g., methyl or propyl-p-hydroxybenzoates or sorbic acid), and the like. Stabilizing agents such as antioxidants (BHA, BHT, propyl gallate, sodium ascorbate, citric acid) can also be added to stabilize the dosage forms. For example, solutions may contain from about 0.2% to about 20% by weight of the active substance, with the balance being sugar and mixture of ethanol, water, glycerol and propylene glycol. Optionally, such liquid formulations may contain coloring agents, flavoring agents, saccharine and carboxymethyl-cellulose as a thickening agent or other excipients.

[0064] In another embodiment, a therapeutically effective amount of the active substance is administered in an oral solution containing a preservative, a sweetener, a solubilizer, and a solvent. The oral solution may include one or more buffers, flavorings, or additional excipients. In a further embodiment, a peppermint or other flavoring is added to the oral liquid formulation.

[0065] For administration by inhalation, the compositions may be conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. In the case of a pressurized aerosol, the dosage unit can be determined by providing a valve to deliver a metered amount. Capsules and cartridges of, e.g.,

gelatin for use in an inhaler or insufflator can be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[0066] Solutions for parenteral applications by injection may be prepared in an aqueous solution of a water-soluble pharmaceutically acceptable salt of the active substances, preferably in a concentration of from about 0.5% to about 10% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may conveniently be provided in various dosage unit ampoules.

[0067] The formulations of the invention may be delivered parenterally, i.e., by intravenous (i.v.), intracerebroventricular (i.c.v.), subcutaneous (s.c.), intraperitoneal (i.p.), intramuscular (i.m.), subdermal (s.d.), or intradermal (i.d.) administration, by direct injection, via, for example, bolus injection or continuous infusion. Formulations for injection can be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. Alternatively, the active ingredient may be in powder form for reconstitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[0068] The invention also provides a pharmaceutical pack or kit comprising one or more containers containing the active substances (i.e., memantine and/or, for example, pioglitazone) and, optionally, more of the ingredients of the formulation. In a specific embodiment, the compositions are provided as oral solutions (2 mg/ml) for administration with the use of a 2 teaspoon capacity syringe (dosage KORC®). Each oral syringe has blue hatch marks for measurement, with lines on the right side of the syringe (tip down) representing tsp units, and those on the left representing ml units.

[0069] The optimal therapeutically effective amount may be determined experimentally, taking into consideration the exact mode of administration, from in which the drug is administered, the indication toward which the administration is

directed, the subject involved (e.g., body weight, health, age, sex, etc.), and the preference and experience of the physician or veterinarian in charge.

[0070] Dosage units for rectal application may be solutions or suspensions or may be prepared in the form of suppositories or retention enemas comprising the active substances in a mixture with a neutral fatty base, or gelatin rectal capsules comprising the active substances in admixture with vegetable oil or paraffin oil.

[0071] Toxicity and therapeutic efficacy of the compositions of the invention may be determined by standard pharmaceutical procedures in experimental animals, e.g., by determining the LD<sub>50</sub> (the dose lethal to 50% of the population) and the ED<sub>50</sub> (the dose therapeutically effective in 50% of the population). The dose ratio between therapeutic and toxic effects is the therapeutic index and it may be expressed as the ratio LD<sub>50</sub>/ED<sub>50</sub>. Compositions that exhibit large therapeutic indices are preferred.

[0072] Suitable daily doses of the active compounds of the invention in therapeutic treatment of humans are about 0.01-10 mg/kg bodyweight on peroral administration and 0.001-10 mg/kg bodyweight on parenteral administration. For example, for adults, suitable daily doses of memantine (e.g. memantine hydrochloride) are within the range from about 1 mg to about 200 mg per day, such as from about 5 mg to about 80 mg, from about 10 mg to about 40 mg, such as 5 mg, 10 mg, 15 mg, or 20 mg, per day. For pediatric subjects aged 4-14, memantine (e.g. memantine hydrochloride) may be administered as an oral, liquid dosage form, at about 0.5 mg/day, up to a maximum dose of 10 mg/day. Suitable daily doses for glitazones are within the range of from about 1 to about 1000 mg per day. For example, suitable daily dosages for pioglitazone (e.g., pioglitazone hydrochloride) are within the range of 5 mg to 200 mg per day, such as from about 15 mg to 45 mg per day; suitable daily dosages for rosiglitazone (e.g., rosiglitazone maleate) are within the range of 1 mg to 100 mg per day, such as from 5 mg to 10 mg per day.

[0073] Treatment duration may be short-term, e.g., several weeks (for example 8-14 weeks), or long-term until the attending physician deems further administration no longer is necessary.

## EXAMPLES

[0074] The following examples illustrate the invention without limiting its scope.

### **EXAMPLE 1: Evaluation of Memantine in Combination with Pioglitazone for the Treatment of Alzheimer's Disease**

[0075] The objective of this pilot project is to conduct a clinical trial to assess the efficacy of a combination comprising memantine and pioglitazone as a treatment for Alzheimer's disease. Patients treated with a combination comprising memantine and pioglitazone may be expected to demonstrate beneficial therapeutic effects which are substantially greater than the therapeutic effects provided by memantine monotherapy.

#### **Study Design**

[0076] The primary objective of this study is to investigate the effect of memantine in combination with pioglitazone on disease progression (as measured by SIB and ADCS-ADL) in patients suffering from Alzheimer's disease.

#### **Statistical Procedures and Populations for Analysis**

[0077] In order to be eligible to participate in the study, patients must meet the following criteria:

- Diagnosis of possible or probable Alzheimer's disease based on NINCDS-ADRDA criteria
- Presence of a caregiver (friend or relative) who can assume responsibility for medication compliance, can accompany the patient to all visits, and rate patient's condition
- Signed informed consent from both the patient (or surrogate) and caregiver
- A Mini Mental State Exam Score (MMSE) of 5 to 14
- An MRI or CT scan consistent with the diagnosis of probable Alzheimer's disease
- Daily memantine therapy for the past 6 months (stable dose for the past three months)

[0078] Patients meeting any of the following criteria are excluded from the study:

- Diagnosis of a non-Alzheimer primary dementia (e.g., vascular dementia)
- Current institutionalization (skilled nursing or assisted living facility)
- Diagnosis of major depression, delirium, substance abuse or dependency, schizophrenia, or delusional disorder as defined by DSM-IV
- Presence of any uncontrolled systemic illness that would interfere with participation in the study
- Enrollment in another interventional clinical trial
- Type I or secondary diabetes mellitus
- Type II diabetes mellitus treated with insulin sulfonylurea or glipizide
- History or evidence of congestive heart failure, clinically significant peripheral edema or anemia

[0079] The scheduled visits for evaluation of each patient are as follows:

[0080] **Visit 1** (initial screening): After signing the consent form, the subject undergoes an evaluation, in which primary and secondary parameters are evaluated. Patient eligibility for study is evaluated via review of inclusion/exclusion criteria with the subject and caregiver.

[0081] **Visit 2** (baseline): Subject is evaluated for study eligibility based on a review of the inclusion/exclusion criteria. Study procedures as well as concomitant medications are reviewed with the subject and caregiver. Subject is enrolled in the study and medication is dispensed as described below.

[0082] **Visits 3-6**: These visits occur four, eight, twelve, and eighteen weeks after baseline. Review of concomitant medications as well as the occurrence of adverse events since the last visit are conducted with subject and caregiver. Primary and secondary parameters are evaluated. Medication is dispensed as described below.

[0083] **Visit 7**: This visit occurs twenty-four weeks after baseline. Change from baseline in SIB and ADCS-ADL Inventory scores as well as secondary parameters are evaluated.

#### **Administration of Memantine/Pioglitazone combination**

##### **Memantine**

[0084] Memantine hydrochloride is administered as commercially available tablets containing 5 mg memantine at a dose of 20 mg per day.

##### **Pioglitazone**

[0085] Pioglitazone hydrochloride is administered as commercially available tablets containing 15 mg pioglitazone at a dose of 15-45 mg per day. Placebo is administered as matching tablets.

**Efficacy**

[0086] Patients are evaluated using functional scales as well as quality of life scales.

[0087] Primary Outcome

- Change from baseline in Severe Impairment Battery (SIB) Test and AD Cooperative Study – Activities of Daily Living (ADCS-ADL) Inventory scores at Week 24

[0088] Secondary Outcomes

- (CIBIC-plus) rating at Week 24

**Data Analysis**

[0089] Comparisons between the memantine/pioglitazone and memantine/placebo groups for primary efficacy parameters were made using a two-way analysis of covariance (ANCOVA). Primary efficacy analyses focused on the scores obtained at the end of Week 24, examining the change from baseline for the SIB and ADCS-ADL. For the CIBIC-Plus score, the Cochran-Mantel-Haenszel statistic using modified ridit scores (the van Elteren test) was applied to compare the distributions between memantine/pioglitazone and memantine/placebo groups.

[0090] All efficacy analyses were based upon the randomized patients who took at least one dose of study medication and who had at least one post-baseline primary efficacy assessment. All statistical tests were two-sided, and a p value  $\leq 0.05$  was considered statistically significant. Primary analyses were performed on the ITT population using the Last Observation Carried Forward (LOCF) approach at Week



24. In these analyses, the last observed value before the missing value was carried forward to impute the missing value. The observed cases (OC) approach was used for supportive analyses, where only the observed values at each visit were used for analyses. The LOCF approach was also used at each visit for supportive analyses.

[0091] For the change from baseline in the total SIB and ADCS-ADL Inventory scores at Week 24, the comparison between memantine/pioglitazone and memantine/placebo was performed using two-way analysis of covariance (ANCOVA) with treatment group and center as the two factors, and the baseline scores as covariate. Descriptive statistics were calculated by visit. The CIBIC-plus rating was analyzed using the CMH test, controlling for study center. Descriptive statistics were calculated by visit.

## **Discussion**

[0092] Memantine/pioglitazone combination treatment provides beneficial effects based on measures of cognition, daily functioning, and clinical global status which are substantially greater than the beneficial effects associated with memantine monotherapy.

\* \* \* \* \*

[0093] The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description. Such modifications are intended to fall within the scope of the appended claims.

[0094] All patents, applications, publications, test methods, literature, and other materials cited herein are hereby incorporated by reference.

**CLAIMS**

1. Use of memantine or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in combination with a glitazone in treating neurodegenerative diseases and/or providing neuroprotection.
2. Use as claimed in claim 1 wherein the neurodegenerative disease is selected from Alzheimer's disease, stroke, multiple sclerosis, progressive supranuclear palsy, schizophrenia, Huntington's disease and amyotrophic lateral sclerosis.
3. Use as claimed in claim 2 wherein the neurodegenerative disease is Alzheimer's disease.
4. Use as claimed in any preceding claim wherein the glitazone is selected from pioglitazone, troglitazone, rosiglitazone, ciglitazone, englitazone, darglitazone, rivoglitazone, isaglitazone, KRP 297, T 174, NP 0110 and pharmaceutically acceptable salts of any of the foregoing.
5. Use as claimed in claim 4 wherein the glitazone is selected from pioglitazone and pharmaceutically acceptable salts thereof.
6. Use of memantine or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment of Alzheimer's disease in combination with pioglitazone or a pharmaceutically acceptable salt thereof.
7. Use as claimed in claim 6 wherein the medicament is manufactured for simultaneous coadministration of said memantine or salt thereof and said pioglitazone or salt thereof.

8. Use as claimed in claim 7 wherein the medicament is manufactured as a unitary dosage form comprising said memantine or salt thereof and said pioglitazone or salt thereof.
9. Use as claimed in claim 8 wherein the medicament is manufactured for administration of said memantine or salt thereof at a dose of 5 to 150 mg memantine per day and said pioglitazone or salt thereof at a dose of 5 to 150 mg pioglitazone per day.
10. Use as claimed in claim 9 wherein said doses are 5 to 80 mg memantine per day and 5 to 100 mg pioglitazone per day.
11. Use as claimed in claim 10 wherein said doses are 10 to 40 mg memantine per day and 15 to 45 mg pioglitazone per day.
12. Use as claimed in claim 11 wherein said doses are 20 mg memantine per day and 45 mg pioglitazone per day.
13. Use as claimed in any one of claims 8 to 12 wherein the medicament is manufactured to provide said memantine or salt thereof and said pioglitazone or salt thereof once a day, twice a day (b.i.d.), or three times a day.
14. Use as claimed in any one of claims 8 to 13 wherein the medicament is manufactured to provide said memantine or salt thereof and said pioglitazone or salt thereof in an immediate release formulation.
15. Use as claimed in any one of claims 8 to 13 wherein the medicament is manufactured to provide said memantine or salt thereof and said pioglitazone or salt thereof in a modified release formulation.

16. Use as claimed in any preceding claim wherein memantine is employed as its hydrochloride salt.
17. A composition comprising memantine or a pharmaceutically acceptable salt thereof and a glitazone.
18. The composition of claim 17 wherein the glitazone is selected from pioglitazone and pharmaceutically acceptable salts thereof.
19. The composition of claim 18 further comprising a pharmaceutically acceptable carrier.
20. The composition of claim 19 which is a solid oral dosage form.
21. A method of treating a neurodegenerative disease and/or providing neuroprotection in a subject in need thereof, comprising administering a first amount of memantine, or a pharmaceutically acceptable salt thereof, and a second amount of a glitazone, wherein the first and second amounts in combination are effective in treating the neurodegenerative disease.
22. Memantine or a pharmaceutically acceptable salt thereof for use with a glitazone in treating a neurodegenerative disease and/or providing neuroprotection.

# INTERNATIONAL SEARCH REPORT

International application No  
PCT/EP2008/008400

## A. CLASSIFICATION OF SUBJECT MATTER

INV. A61K31/13 A61K31/425 A61P25/28

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)

A61K A61P

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 practical, search terms used)

EPO-Internal, WPI Data, BIOSIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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☒ 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
- \*E\* earlier document but published on or after the international filing date
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- \*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

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

Date of the actual completion of the international search

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## INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2008/008400

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Information on patent family members

International application No

PCT/EP2008/008400

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