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(54) Title: COMBINATION COMPRISING A NEUROPROTECTING AGENT AND AN AGENT BINDING TO GADPH AND PHARMACEUTICAL USE THEREOF

(57) Abstract: The present invention relates to combinations suitable for the treatment of neurodegenerative disorders, in particular amyotrophic lateral sclerosis, Parkinson's disease, and Alzheimer's Disease, comprising (a) a neuroprotectant having an inhibitory effect on glutamate release or the effect of inactivation of voltage-dependent sodium channels or the ability to interfere with intracellular events that follow transmitter binding at excitatory amino acid receptors, especially selected from riluzole, lubeluzole, lubeluzole-N-oxide and 6-hydroxylubeluzole, and (b) an active ingredient binding to GADPH; to their use for the preparation of a medicament for the treatment of neurodegenerative disorders; to commercial packages comprising said combinations; to pharmaceutical composition comprising said combinations; and to a method of treating a warm-blooded animal having neurodegenerative disorders.

Combination Comprising a Neuroprotecting Agent and an Agent Binding to GADPH and Pharmaceutical Use thereof

The present invention relates to combinations suitable for the treatment of neuro-degenerative disorders, in particular amyotrophic lateral sclerosis (ALS), Parkinson's disease (PD), and Alzheimer's Disease (AD).

Surprisingly, it has been found that the effect of a combination which comprises (a) a neuroprotectant having an inhibitory effect on glutamate release or the effect of inactivation of voltage-dependent sodium channels or the ability to interfere with intracellular events that follow transmitter binding at excitatory amino acid receptors, and (b) an active ingredient binding to GADPH is greater than the additive effect of the single components (a) or (b). In particular, it has been found that the effect of a combination which comprises riluzole and a dibenzo-oxepine on neurodegenerative disorders is greater than the additive effect of the single drugs. Furthermore, the combinations disclosed herein can be used to treat neurodegenerative disorders, which are refractory to mono therapy employing one of the combination partners alone.

Hence, the invention relates to a combination, such as a combined preparation or pharmaceutical composition, which comprises (a) a neuroprotectant having an inhibitory effect on glutamate release or the effect of inactivation of voltage-dependent sodium channels or the ability to interfere with intracellular events that follow transmitter binding at excitatory amino acid receptors, and (b) an active ingredient binding to GADPH, in particular a combination comprising riluzole and a dibenzo-oxepine, in which the active ingredients are present in each case in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier; for simultaneous, separate or sequential use, especially in the treatment of neurodegenerative disorders.

In particular, the invention relates to a combination suitable for synergistic action of the active components against neurodegenerative disorders which consists of synergistically effective amounts of (a) at least one neuroprotectant having an inhibitory effect on glutamate release or the effect of inactivation of voltage-dependent sodium channels or the ability to interfere with intracellular events that follow transmitter binding at excitatory amino acid receptors, and (b) at least one active ingredient binding to GADPH, in which the active

ingredients are present in each case in free form or in the form of a pharmaceutically acceptable salt, for simultaneous, separate or sequential use.

The term "neurodegenerative disorders" as used herein includes, but is not restricted to, ALS, PD, cerebral ischemia, AD, glaucoma, Huntington's chorea, fronto temporal lobe dementia, Lewy body dementia, retinitis pigmentosa and other retinal neurodegenerative disorders, mild cognitive impairment, progressive supranuclear palsy or atrophy, multiple sclerosis, multiple system atrophy, spinocerebellar atrophy, and also general, degenerative or diabetic peripheral neuropathies. In particular, the term "neurodegenerative disorders" relates to ALS, PD and AD.

ALS, sometimes called Lou Gehrig's disease, is a rapidly progressive, invariably fatal neurological disease that attacks the nerve cells (neurons) responsible for controlling voluntary muscles. The disease belongs to a group of disorders known as motor neuron diseases, which are characterized by the gradual degeneration and death of motor neurons. The disease causes weakness with a wide range of disabilities. Eventually, all muscles under voluntary control are affected, and patients lose their strength and the ability to move their arms, legs, and body. Most people with ALS die from respiratory failure, usually within 3 to 5 years from the onset of symptoms. ALS is one of the most common neuromuscular diseases worldwide, and people of all races and ethnic backgrounds are affected. ALS most commonly strikes people between 40 and 60 years of age, but younger and older people also can develop the disease. In 90 to 95 percent of all ALS cases, the disease occurs apparently at random with no clearly associated risk factors. Patients do not have a family history of the disease, and their family members are not considered to be at increased risk for developing ALS. About 5 to 10 percent of all ALS cases are inherited. Some cases result from a specific genetic defect that leads to mutation of the enzyme known as superoxide dismutase 1 (SOD1). The earliest symptoms of ALS may include twitching, cramping, or stiffness of muscles; muscle weakness affecting an arm or a leg; slurred and nasal speech; or difficulty chewing or swallowing. In some cases, symptoms initially affect one of the legs, and patients experience awkwardness when walking or running or they notice that they are tripping or stumbling more often. Other patients notice speech problems. To be diagnosed with ALS, patients must have signs and symptoms of both upper and lower motor neuron damage that cannot be attributed to other causes.

PD is a chronic, degenerative neurological disorder that affects both voluntary and involuntary movement. Tremor, rigidity and freezing in place, pain, muscle cramps, swallowing difficulty, balance problems and dementia are only some of the symptoms of Parkinson's which can cause severe debilitation. There is no cure at present. The various treatment options can offer Parkinson's patients temporary relief from symptoms.

AD is a progressive neurodegenerative disease characterized by distinct pathologies including fibrillary tangles, neuritic plaques, neuronal atrophy, dendritic pruning and neuronal death. AD is causing impaired memory, thinking and behavior.

In one embodiment of the invention, the disease to be treated is ALS, especially ALS which is caused by a genetic defect that leads to mutation of the superoxide dismutase 1. In another embodiment of the invention, the disease to be treated is PD.

The term "riluzole" as used herein refers to 2-amino-6-(trifluoromethoxy) benzothiazole. In a broader sense of the invention, the term "riluzole" also comprises active ingredients having at least one pharmacological property also observed with riluzole selected from an inhibitory effect on glutamate release, inactivation of voltage-dependent sodium channels and the ability to interfere with intracellular events that follow transmitter binding at excitatory amino acid receptors. The use of riluzole in ALS is described in US 5,527,814, the compound and its preparation is disclosed in EP 050551. Other neuroprotectant compounds can be prepared as described, e.g., by Yagupolskii et al in Zhurnal Obschei Khimii 33 (7), 2301-7 (1963).

The term "dibenzo-oxepine" as used herein includes, but is not limited to, the compounds disclosed in US 5,780, 500, the disclosure of which is incorporated by reference into the present patent specification, in particular the claimed chemical compounds and final products of the working examples.

In a broader sense of the invention, a suitable combination comprises an active ingredient binding to GADPH, like the dibenzo-oxepines mentioned herein, and a neuroprotectant having an inhibitory effect on glutamate release or the effect of inactivation of voltage-dependent sodium channels or the ability to interfere with intracellular events that follow

transmitter binding at excitatory amino acid receptors, in particular selected from the group consisting of riluzole, lubeluzole, lubeluzole-N-oxide and 6-hydroxylubeluzole.

Preferably, the active ingredient binding to GADPH is selected from the dibenzo-oxepines mentioned herein, rasagiline, selegiline and desmethyl-deprenyl.

In a preferred embodiment of the present invention, the combination comprises the dibenzo-oxepine N-methyl-N-2-propynyldibenz[b,f]oxepin-10-methanamine, also disclosed in US 5,780, 500. In a further preferred embodiment of the invention, the combination comprises a pharmaceutically acceptable salt of N-methyl-N-2-propynyldibenz[b,f]oxepin-10-methanamine, especially the hydrogen maleate, as disclosed, e.g., in WO97/45422.

Riluzole can be administered, e.g., in the form as marketed, e.g. under the trademark RILUTEK™. Dibenzo-oxepines may be administered, e.g., in the form as described in US 5,780, 500.

The structure of the active ingredients identified by code nos., generic or trade names may be taken from the actual edition of the standard compendium "The Merck Index" or from databases, e.g. Patents International (e.g. IMS World Publications). The corresponding content thereof is hereby incorporated by reference. Any person skilled in the art is fully enabled to identify the active ingredients and, based on these references, likewise enabled to manufacture and test the pharmaceutical indications and properties in standard test models, both *in vitro* and *in vivo*.

The term "a combined preparation", as used herein defines especially a "kit of parts" in the sense that the first and second active ingredient as defined above can be dosed independently or by use of different fixed combinations with distinguished amounts of the ingredients, i.e., simultaneously or at different time points. The parts of the kit of parts can then, e.g., be administered simultaneously or chronologically staggered, that is at different time points and with equal or different time intervals for any part of the kit of parts. Very preferably, the time intervals are chosen such that the effect on the treated disease in the combined use of the parts is larger than the effect which would be obtained by use of only any one of the active ingredients. The ratio of the total amounts of the active ingredient 1 to the active ingredient 2 to be administered in the combined preparation can be varied, e.g., in

order to cope with the needs of a patient sub-population to be treated or the needs of the single patient which different needs can be due to age, sex, body weight, etc. of the patients. Preferably, there is at least one beneficial effect, e.g., a mutual enhancing of the effect of the first and second active ingredient, in particular a synergism, e.g. a more than additive effect, additional advantageous effects, less side effects, a combined therapeutic effect in a non-effective dosage of one or both of the first and second active ingredient, and especially a strong synergism the first and second active ingredient.

It will be understood that in the discussion of methods, references to the active ingredients are meant to also include the pharmaceutically acceptable salts. If these active ingredients have, for example, at least one basic center, they can form acid addition salts. Corresponding acid addition salts can also be formed having, if desired, an additionally present basic center. The active ingredients having an acid group (for example COOH) can also form salts with bases. The active ingredient or a pharmaceutically acceptable salt thereof may also be used in form of a hydrate or include other solvents used for crystallization.

A pharmaceutical combination which comprises riluzole and a dibenzo-oxepine, in which the active ingredients are present in each case in free form or in the form of a pharmaceutically acceptable salt, if at least one salt-forming group is present, will be referred to hereinafter as a COMBINATION OF THE INVENTION.

Surprisingly it was found that the administration of a COMBINATION OF THE INVENTION results in a beneficial, especially a synergistic, therapeutic effect or in other surprising beneficial effects, e.g. less side effects or a slower progression of the disease, e.g. documented by a higher survival rate, a delay to use mechanical help to maintain lung function, improved or maintained functional parameters or Quality of Life benefits, compared to a mono therapy applying only one of the pharmaceutically active ingredients used in the COMBINATION OF THE INVENTION.

The pharmacological activity of a COMBINATION OF THE INVENTION may, for example, be evidenced in preclinical studies known as such.

The pharmacological activity of a COMBINATION OF THE INVENTION may, for example, be demonstrated in a clinical study. Such clinical studies are preferably randomized, double-

blind, clinical studies in patients with ALS with either familial or sporadic ALS. Such studies demonstrate, in particular, the synergism of the active ingredients of the COMBINATIONS OF THE INVENTION. The beneficial effects on ALS can be determined directly through the results of these studies, e.g. by the time to tracheostomy or death in patients taking the COMBINATION OF THE INVENTION compared to placebo, or by changes in the study design which are known as such to a person skilled in the art. The studies are, in particular, suitable to compare the effects of a mono therapy using the active ingredients and a COMBINATION OF THE INVENTION.

A further benefit is that lower doses of the active ingredients of the COMBINATION OF THE INVENTION can be used, for example, that the dosages need not only often be smaller but are also applied less frequently, or can be used in order to diminish the incidence of side effects, e.g. those observed with riluzole, e.g. nausea, an increase of the liver transaminase level, head aches, vomiting, dizziness, pancreatitis or neutropenia. This is in accordance with the desires and requirements of the patients to be treated. The COMBINATIONs OF THE INVENTION can be used, in particular, for the treatment of ALS, AD or PD which is refractory to mono therapy.

It is one objective of this invention to provide a pharmaceutical composition comprising a quantity, which is jointly therapeutically effective against neurodegenerative disorders, comprising the COMBINATION OF THE INVENTION and at least one pharmaceutically acceptable carrier. In this composition, the first and second active ingredient can be administered together, one after the other or separately in one combined unit dosage form or in two separate unit dosage forms. The unit dosage form may also be a fixed combination. In particular, the present invention provides a pharmaceutical composition consisting of a quantity, which is jointly therapeutically effective against neurodegenerative disorders, of (a) at least one neuroprotectant having an inhibitory effect on glutamate release or the effect of inactivation of voltage-dependent sodium channels or the ability to interfere with intracellular events that follow transmitter binding at excitatory amino acid receptors, and (b) at least one active ingredient binding to GADPH, in which the active ingredients are present in each case in free form or in the form of a pharmaceutically acceptable salt and at least one pharmaceutically acceptable carrier.

The pharmaceutical compositions according to the invention can be prepared in a manner known per se and are those suitable for enteral, such as oral or rectal and parenteral administration to mammals (warm-blooded animals), including man, comprising a therapeutically effective amount of at least one pharmacologically active ingredient, alone or in combination with one or more pharmaceutically acceptable carries, especially suitable for enteral or parenteral application. The preferred route of administration of the dosage forms of the present invention is orally.

The novel pharmaceutical composition contain, for example, from about 10 % to about 100 %, preferably from about 20 % to about 60 %, of the active ingredients. Pharmaceutical preparations for the combination therapy for enteral or parenteral administration are, for example, those in unit dosage forms, such as sugar-coated tablets, eye-drops, tablets, capsules or suppositories, and furthermore ampoules. If not indicated otherwise, these are prepared in a manner known per se, for example by means of conventional mixing, granulating, sugar-coating, dissolving or lyophilizing processes. It will be appreciated that the unit content of active ingredient or ingredients contained in an individual dose of each dosage form need not in itself constitute an effective amount since the necessary effective amount can be reached by administration of a plurality of dosage units.

In preparing the compositions for oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils or alcohols; or carriers such as starches, sugars, microcristalline cellulose, diluents, granulating agents, lubricants, binders, disintegrating agents and the like in the case of oral solid preparations such as, for example, powders, capsules and tablets. Because of their ease of administration, tablets and capsules represent the most advantageous oral dosage unit form in which case solid pharmaceutical carriers are obviously employed.

In particular, a therapeutically effective amount of each of the active ingredients of the COMBINATION OF THE INVENTION may be administered simultaneously or sequentially and in any order, and the components may be administered separately or as a fixed combination. For example, the method of treatment of diseases according to the invention may comprise (i) administration of the first active ingredient in free or pharmaceutically acceptable salt form and (ii) administration of the second active ingredient in free or pharmaceutically acceptable salt form, simultaneously or sequentially in any order, in jointly

therapeutically effective amounts, preferably in synergistically effective amounts, e.g. in daily dosages corresponding to the amounts described herein. The individual active ingredients of the COMBINATION OF THE INVENTION can be administered separately at different times during the course of therapy or concurrently in divided or single combination forms. Furthermore, the term administering also encompasses the use of a prodrug of an active ingredient that convert *in vivo* to the active ingredient as well as the use of active metabolites. The instant invention is therefore to be understood as embracing all such regimes of simultaneous or alternating treatment and the term "administering" is to be interpreted accordingly.

Furthermore, the present invention relates to the use of a COMBINATION OF THE INVENTION for the preparation of a medicament for the treatment of neurodegenerative disorders.

Additionally, the present invention provides a method of treating a warm-blooded animal having neurodegenerative disorders comprising administering to the animal a COMBINATION OF THE INVENTION in a quantity which is jointly therapeutically effective against said neurodegenerative disorders and in which the compounds can also be present in the form of their pharmaceutically acceptable salts.

Moreover, the present invention provides a commercial package comprising as active ingredients COMBINATION OF THE INVENTION, together with instructions for simultaneous, separate or sequential use thereof in the treatment of neurodegenerative disorders, preferably amyotrophic lateral sclerosis.

In one preferred embodiment of the invention, the COMBINATION OF THE INVENTION is used for the treatment of neurodegenerative disorders which are refractory to monotherapy.

The effective dosage of each of the active ingredients employed in the COMBINATION OF THE INVENTION may vary depending on the particular compound or pharmaceutical composition employed, the mode of administration, the severity of the neurodegenerative disorder being treated. Thus, the dosage regimen the COMBINATION OF THE INVENTION is selected in accordance with a variety of factors including the route of administration and the renal and hepatic function of the patient. A physician, clinician or veterinarian of ordinary

skill can readily determine and prescribe the effective amount of the single active ingredients required to prevent, counter or arrest the progress of the condition. Optimal precision in achieving concentration of the active ingredients within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the active ingredients' availability to target sites. This involves a consideration of the distribution, equilibrium, and elimination of the active ingredients.

When the combination partners employed in the COMBINATION OF THE INVENTION are applied in the form as marketed as single drugs, their dosage and mode of administration can take place in accordance with the information provided on the packet leaflet of the respective marketed drug in order to result in the beneficial effect described herein, if not mentioned herein otherwise. In particular, riluzole can be applied in a dosage of 20 to 50 mg, preferably about 25 to 35 mg, every 12 hours. RILUTEK tablets should be taken at least an hour before, or two hours after, a meal to avoid a food-related decrease in bioavailability.

What is claimed is:

1. A combination comprising (a) a neuroprotectant having an inhibitory effect on glutamate release or the effect of inactivation of voltage-dependent sodium channels or the ability to interfere with intracellular events that follow transmitter binding at excitatory amino acid receptors, and (b) an active ingredient binding to GADPH, in which the active ingredients are present in each case in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier; for simultaneous, separate or sequential use.

2. A combination suitable for synergistic action of the active components against neurodegenerative disorders which consists of synergistically effective amounts of a) at least one neuroprotectant having an inhibitory effect on glutamate release or the effect of inactivation of voltage-dependent sodium channels or the ability to interfere with intracellular events that follow transmitter binding at excitatory amino acid receptors, and (b) at least one active ingredient binding to GADPH, in which the active ingredients are present in each case in free form or in the form of a pharmaceutically acceptable salt; for simultaneous, separate or sequential use.

3. Combination according to claim 1 or 2 wherein the neuroprotectant is selected from riluzole, lubeluzole, lubeluzole-N-oxide and 6-hydroxylubeluzole.

4. Combination according to claim 1 or 2 comprising (a) the neuroprotectant riluzole and (b) a dibenzo-oxepine.

5. Combination according to claim 1 or 2 which is a combined preparation or a Pharmaceutical composition.

6. Combination according to any one of claims 1 to 5 comprising N-methyl-N-2-propynyldibenz[b,f]oxepin-10-methanamine or a pharmaceutically acceptable salt thereof.

7. Combination according to any one of claims 1 to 6 for simultaneous, separate or sequential use in the treatment of neurodegenerative disorders.

8. Combination according to any one of claims 1 to 6 for simultaneous, separate or sequential use in the treatment of Parkinson's disease.

9. Combination according to any one of claims 1 to 6 for simultaneous, separate or sequential use in the treatment of amyotrophic lateral sclerosis.

10. Combination according to any one of claims 1 to 6 for simultaneous, separate or sequential use in the treatment of Alzheimer's Disease.

11. Method of treating a warm-blooded animal having neurodegenerative disorders comprising administering to the animal a combination according to any one of claims 1 to 6 in a quantity which is jointly therapeutically effective against said neurodegenerative disorders and in which the compounds can also be present in the form of their pharmaceutically acceptable salts.

12. Method according to claim 11 wherein the neurodegenerative disorder is amyotrophic lateral sclerosis.

13. Method according to claim 11 wherein the neurodegenerative disorder is Parkinson's disease.

14. Method according to claim 11 wherein the neurodegenerative disorder is Alzheimer's disease.

15. A pharmaceutical composition comprising a quantity, which is jointly therapeutically effective against neurodegenerative disorders, of a pharmaceutical combination according to any one of claims 1 to 6 and at least one pharmaceutically acceptable carrier.

16. A pharmaceutical composition consisting of a quantity, which is jointly therapeutically effective against neurodegenerative disorders, of a) at least one neuroprotectant having an inhibitory effect on glutamate release or the effect of inactivation of voltage-dependent sodium channels or the ability to interfere with intracellular events that follow transmitter binding at excitatory amino acid receptors, and (b) at least one active ingredient binding

to GADPH, in which the active ingredients are present in each case in free form or in the form of a pharmaceutically acceptable salt and at least one pharmaceutically acceptable carrier.

17. Use of a combination according to any one of claims 1 to 6 for the preparation of a medicament for the treatment of neurodegenerative disorders.

18. Use of a combination according to any one of claims 1 to 6 for the preparation of a medicament for the treatment of Parkinson's disease, Alzheimer's Disease or amyotrophic lateral sclerosis.

19. Use according to claim 17 or 18 wherein the disease is refractory to monotherapy.

20. A commercial package comprising a combination according to any one of claim 1 to 6 together with instructions for simultaneous, separate or sequential use thereof in the treatment of neurodegenerative disorders, preferably amyotrophic lateral sclerosis.