A COMBINATION PHARMACEUTICAL COMPOSITION AND METHODS OF TREATING DISEASES OR CONDITIONS ASSOCIATED WITH THE CARDIOVASCULAR SYSTEM

FIELD

The present invention relates to the field of medicine and can be used for the treatment and prevention of diseases of the cardiovascular system.

BACKGROUND

Nitric oxide (NO) is a cellular signaling molecule which plays a role in many biological processes including the relaxation of vascular and non-vascular tissue. Nitric oxide is synthesized from L-arginine by nitric oxide synthase (NO synthase). NO synthase occurs in different isoforms, including a constitutive form (cNOS) and an inducible form (iNOS). The constitutive form is present in normal endothelial cells, neurons and some other tissues. Formation of nitric oxide by the constitutive form in endothelial cells is thought to play an important role in normal blood pressure regulation.

Angiotensin is a protein that causes blood vessels to constrict, and drives blood pressure up and stimulates the release of aldosterone from the adrenal cortex. Angiotensin is part of the renin-angiotensin system (a hormone system that regulates blood pressure and water (fluid) balance) which is a major target for drugs that lower blood pressure. Angiotensin II receptor type 1 (AT1) is believed to mediate the key effects of angiotensin II.

The therapeutic effect of an extremely diluted (or ultra-low) form of antibodies potentized by homeopathic technology has been discovered by the inventor of the present patent application, Dr. Oleg I. Epshtein. U.S. Patent No. 7,582,294 discloses a medicament for treating Benign Prostatic Hyperplasia or prostatitis by administration of a homeopathically activated form of antibodies to prostate specific antigen (PSA). U. S. Patent Publication No. 2010/0260742 discloses a homeopathically potentized form of antibodies to a C-terminal fragment of the angiotensin II AT1 receptor. The

homeopathically potentized form of antibodies to a C-terminal fragment of the angiotensin II AT1 receptor is marketed in the Russian Federation and other countries under the name Kardos®. U.S. Patent No. 7,700,096 discloses and claims a homeopathically potentized form of antibodies to endothelial NO-synthase. The homeopathically potentized form of antibodies to endothelial NO-synthase is marketed in the Russian Federation and other countries under the name Impaza®.

There is a continuing need for new drug products with desired therapeutic efficacy for treatment of diseases and disorder of the cardiovascular system.

SUMMARY

In an embodiment the disclosure provides a pharmaceutical composition for administration to a patient suffering from at least one symptom of a cardiovascular condition, said composition comprising a) an activated-potentiated form of an antibody to angiotensin II AT1 receptor, and b) an activated-potentiated form of an antibody to endothelial NO-synthase.

In a first aspect, there is provided a combination pharmaceutical composition for administration to a patient associated with at least one symptom of at least one condition selected from the group consisting of chronic heart failure, asthenia, vegetative vascular dystonia, anxiety associated with chronic heart failure, depression associated with chronic heart failure and hypertension, the combination pharmaceutical composition comprising a) an activated-potentiated form of an antibody to angiotensin II AT1 receptor, and b) an activated-potentiated form of an antibody to endothelial NO-synthase, the activated potentiated forms produced by homeopathic technology.

In one variant of this embodiment of the disclosure a pharmaceutical composition for administration to a patient suffering from at least one symptom of a cardiovascular condition comprises a) an activated-potentiated form of an antibody to a C-terminal fragment of angiotensin II AT1 receptor, and b) an activated-potentiated form of an antibody to endothelial NO-synthase.

Preferably, the pharmaceutical composition of this embodiment is administered to patients with cardiovascular condition(s) associated with a reduced quality of life, wherein the administration of said pharmaceutical composition to said patient improves said quality of life of said patient.

Various variants and embodiments of the pharmaceutical composition are contemplated and provided. They may be used in reference to method embodiments and other embodiments disclosed herein. The specific variants and embodiments disclosed herein are set forth in the appended claims. Preferably, the pharmaceutical composition as defined above comprises activated-potentiated forms of polyclonal antibodies. It is also preferred that the process of preparing the pharmaceutical

composition of this embodiment of the disclosure includes successive centesimal dilutions coupled with vertical shaking of every dilution.

In another embodiment, the disclosure provides a method of treating a patient suffering from a reduced overall quality of life associated with at least one symptom of a cardiovascular condition, said method comprising administering to said patient a combination of a) an activated-potentiated form of an antibody to angiotensin II AT1 receptor, and b) an activated-potentiated form of an antibody to endothelial NO-synthase, thereby said administration improves said overall quality of life of said patient. Preferably, the disclosure provides a method of treating a patient suffering from a reduced overall quality of life associated with at least one symptom of a cardiovascular condition, said method comprising administering to said patient a combination of a) an activated-potentiated form of an antibody to a C-terminal fragment of angiotensin II AT1 receptor, and b) an activated-potentiated form of an antibody to endothelial NO-synthase, thereby said administration improves said overall quality of life of said patient. Various variants and embodiments are contemplated. In particular, it is contemplated that the combination of this embodiment of the disclosure is administered concomitantly with administration of an additional therapeutic agent suitable for administration to patients suffering from said at least one symptom of a cardiovascular condition. The non-limiting list of suitable additional agents includes ACE inhibitors, diuretics; β-adrenergic blockers, nitrates, cardiac glycosides, calcium antagonists, hypolipidemic agents, antiaggregants, antihypoxants, and anticoagulants. Bisoprol, enalapril or aspirin are specifically contemplated.

Particularly contemplated is a method of this embodiment of the disclosure in which said patient is administered said composition in the form of a solid unit dosage form comprising said activated-potentiated form of an antibody to a C-terminal fragment of angiotensin II AT1 receptor and said activated-potentiated form of an antibody to endothelial NO-synthase. Preferably, said patient is administered one to two of said unit dosage forms, each administration carried out from once daily to four times daily.

In another embodiment, the disclosure provides a method of treating a patient suffering from chronic heart failure, said method comprising administering to said patient a

combination of a) an activated-potentiated form of an antibody to a C-terminal fragment of angiotensin II AT1 receptor, and b) an activated-potentiated form of an antibody to endothelial NO-synthase. Various variants and embodiments are contemplated. In particular, it is contemplated that the combination of this embodiment of the disclosure is administered concomitantly with administration of an additional therapeutic agent suitable for administration to patients suffering from said at least one symptom of a cardiovascular condition. The non-limiting list of suitable additional agents includes ACE inhibitors, diuretics; β-adrenergic blockers, nitrates, cardiac glycosides, calcium antagonists, hypolipidemic agents, antiaggregants, antihypoxants, and anticoagulants. Bisoprol, enalapril or aspirin are specifically contemplated.

Particularly contemplated is a method of this embodiment of the disclosure in which said patient is administered said composition in the form of a solid unit dosage form comprising said activated-potentiated form of an antibody to a C-terminal fragment of angiotensin II AT1 receptor and said activated-potentiated form of an antibody to endothelial NO-synthase. Preferably, said patient is administered one to two of said unit dosage forms, each administration carried out from once daily to four times daily. In accordance with this embodiment of the disclosure, said patient exhibits statistically significant improvement in rigidity parameters of carotid radial artery segments upon said administration. In accordance with this embodiment of the disclosure, said patient exhibits statistically significant improvement in rigidity parameters of carotid femoral artery segments upon said administration. In accordance with this embodiment of the disclosure, said patient exhibits statistically significant reduction in anxiety associated with said chronic heart failure upon said administration. It is particularly contemplated that said administration of said combination leads to a statistically significant improvement in the The Minnesota Living with Heart Failure questionnaire (MLHFQ) score in a suitable population of said patients in reference to the baseline. It is particularly contemplated that said administration of said combination leads to a statistically significant reduction in the Kansas City Cardiomyopathy Questionnaire total Score in a suitable population of said patients in reference to the baseline. It is particularly contemplated that said administration of said combination leads to a statistically significant improvement in a 6-

minute walking test score in a suitable population of said patients. It is particularly contemplated that said administration of said combination leads to a statistically significant improvement in the Hospital Anxiety and Depression Scale (HADS) total score in a suitable population of said patients. It is particularly contemplated that said administration of said combination leads to said patient exhibiting statistically significant reduction in depression associated with said chronic heart failure upon said administration.

In another embodiment, the disclosure provides a method of treating a patient suffering from asthenia and/or vegetative-vascular dystonia, said method comprising administering to said patient a combination of a) an activated-potentiated form of an antibody to a C-terminal fragment of angiotensin II AT1 receptor, and b) an activated-potentiated form of an antibody to endothelial NO-synthase. Various variants and embodiments are contemplated. In particular, it is contemplated that the combination of this embodiment of the disclosure is administered concomitantly with administration of an additional therapeutic agent suitable for administration to patients suffering from said at least one symptom of a cardiovascular condition. The non-limiting list of suitable additional agents includes ACE inhibitors, diuretics; β-adrenergic blockers, nitrates, cardiac glycosides, calcium antagonists, hypolipidemic agents, antiaggregants, antihypoxants, and anticoagulants. Bisoprol, enalapril or aspirin are specifically contemplated.

It is particularly contemplated in accordance with this embodiment of the disclosure that said patient exhibits statistically significant improvement in rigidity parameters of carotid radial artery segments upon said administration. It is particularly contemplated that said patient exhibits statistically significant improvement in rigidity parameters of carotid femoral artery segments upon said administration. It is particularly contemplated that said patient exhibits statistically significant reduction in mental asthenia upon said administration. Preferably, said administration of said combination leads to a statistically significant reduction in the mental asthenia by the Multidimensional Fatigue Inventory (MFI-20) scale in a suitable population of said patients in reference to the baseline. Preferably, the administration of the combination drug or medicine in accordance with

this embodiment of the disclosure leads to said patient exhibiting statistically significant reduction in general asthenia upon said administration. Preferably, said administration of said combination leads to a statistically significant reduction in the general asthenia by the MFI-20 scale in a suitable population of said patients in reference to the baseline. Preferably, said patient exhibits statistically significant reduction in anxiety associated with said asthenia and/or vegetative vascular dystonia upon said administration. It is preferred that in accordance with this embodiment of the disclosure, said administration of said combination drug or medicine leads to a statistically significant reduction in the trait anxiety as measured by the Spielberg test in a suitable population of said patients in reference to the baseline. Preferably, said patient exhibits statistically significant reduction in depression associated with said asthenia and/or vegetative vascular dystonia upon said administration. It is particularly contemplated that said administration of said combination drug or medicine leads to a statistically significant reduction in depression as measured by the Beck test in a suitable population of said patients in reference to the baseline. Preferably, said patient exhibits statistically significant improvement in brachial artery dilation level upon said administration.

In another embodiment, the disclosure provides a method of treating hypertension comprising administering the combination described herein to a patient in need thereof. Concomitant administration of an additional therapeutic agent selected from the group consisting of ACE inhibitors, diuretics; β-adrenergic blockers, nitrates, cardiac glycosides, calcium antagonists, hypolipidemic agents, antiaggregants, antihypoxants, and anticoagulants is specifically contemplated.

In a second aspect, there is provided a combination pharmaceutical composition for administration to a patient suffering from at least one symptom of chronic heart failure, asthenia, vegetative dystonia, or hypertension, said composition comprising a) an activated-potentiated form of an antibody to angiotensin II AT1 receptor, and b) an activated-potentiated form of an antibody to endothelial NO-synthase, the activated potentiated forms produced by homeopathic technology.

DETAILED DESCRIPTION

The invention is defined with reference to the appended claims. With respect to the claims, the glossary that follows provides the relevant definitions.

The term "antibody" as used herein shall mean an immunoglobulin that specifically binds to, and is thereby defined as complementary with, a particular spatial and polar organization of another molecule. Antibodies as recited in the claims may include a complete immunoglobulin or fragment thereof, may be natural,

polyclonal or monoclonal, and may include various classes and isotypes, such as IgA, IgD, IgE, IgG1, IgG2a, IgG2b and IgG3, IgM, etc. Fragments thereof may include Fab, Fv and $F(ab')_2$, Fab', and the like. The singular "antibody" includes plural "antibodies".

The term "activated-potentiated form" or "potentiated form", respectively, with respect to antibodies recited herein is used to denote a product of homeopathic potentization of any initial solution of antibodies. "Homeopathic potentization" denotes the use of methods of homeopathy to impart homeopathic potency to an initial solution of relevant substance. Although not so limited, 'homeopathic potentization" may involve, for example, repeated consecutive dilutions combined with external treatment, particularly (mechanical) shaking. In other words, an initial solution of antibody is subjected to consecutive repeated dilution and multiple vertical shaking of each obtained solution in accordance with homeopathic technology. The preferred concentration of the initial solution of antibody in the solvent, preferably, water or a water-ethyl alcohol mixture, ranges from about 0.5 to about 5.0 mg/ml. The preferred procedure for preparing each component, i.e. antibody solution, is the use of the mixture of three aqueous or aqueous-alcohol dilutions of the primary matrix solution (mother tincture) of antibodies diluted 100^{12}, 100^{30} and 100^{200} times, respectively, which is equivalent to centesimal homeopathic dilutions C12, C30 and C200. Examples of homeopathic potentization are described in U.S. Patent Nos. 7,572,441 and 7,582,294, which are incorporated herein by reference in their entirety and for the purpose stated. While the term "activated-potentiated form" is used in the claims, the term "ultra-low doses" is used in the examples. The term "ultra-low doses" became a term of art in the field of art created by study and use of homeopathically diluted and potentized form of substance. The term "ultra-low dose" or "ultra-low doses" is meant as fully supportive and primarily synonymous with the term 'activated-potentiated" form used in the claims.

In other words, an antibody is in the "activated-potentiated" form when three factors are present. First, the "activated-potentiated" form of the antibody is a product of a preparation process well accepted in the homeopathic art. Second, the

"activated-potentiated" form of antibody must have biological activity determined by methods well accepted in modern pharmacology. And third, the biological activity exhibited by the "activated-potentiated" form of the antibody cannot be explained by the presence of the molecular form of the antibody in the final product of the homeopathic process.

For example, the activated potentiated form of antibodies may be prepared by subjecting an initial, isolated antibody in a molecular form to consecutive multiple dilutions coupled with an external impact, such as mechanical shaking. The external treatment in the course of concentration reduction may also be accomplished, for example, by exposure to ultrasonic, electromagnetic, or other physical factors. V. Schwabe "*Homeopathic medicines*", *M., 1967, U.S. Patents Nos. 7,229,648 and 4,311,897, which* are incorporated by reference in their entirety and for the purpose stated, describe such processes which are well accepted methods of homeopathic potentiation in the homeopathic art. This procedure gives rise to a uniform decrease in molecular concentration of the initial molecular form of the antibody. This procedure is repeated until the desired homeopathic potency is obtained. For the individual antibody, the required homeopathic potency can be determined by subjecting the intermediate dilutions to biological testing in the desired pharmacological model. Although not so limited, 'homeopathic potentization" may involve, for example, repeated consecutive dilutions combined with external treatment, particularly vertical (mechanical) shaking. In other words, an initial solution of antibody is subjected to consecutive repeated dilution and multiple vertical shaking of each obtained solution in accordance with homeopathic technology. The preferred concentration of the initial solution of antibody in the solvent, preferably, water or a water-ethyl alcohol mixture, ranges *from about 0.5 to about 5.0 mg/ml. The preferred procedure for preparing each* component, i.e. antibody solution, is the use of the mixture of three aqueous or aqueous-alcohol dilutions of the primary matrix solution (mother tincture) of antibodies diluted 100^{12}, 100^{30} and 100^{200} times, respectively, which is equivalent to centesimal homeopathic dilutions C12, C30 and C200 or the mixture of three aqueous or aqueous-alcohol dilutions of the primary matrix solution (mother tincture)

of antibodies diluted 100^{12}, 100^{30} and 100^{50} times, respectively, which is equivalent to centesimal homeopathic dilutions C12, C30 and C50. Examples of how to obtain the desired potency are also provided, for example, in U.S. Patents Nos. 7,229,648 and 4,311,897, which are incorporated by reference for the purpose stated. The procedure applicable to the "activated potentiated" form of the antibodies described herein is described in more detail below.

There has been a considerable amount of controversy regarding homeopathic treatment of human subjects. While the present invention relies on accepted homeopathic processes to obtain the "activated-potentiated" form of antibodies, it does not rely solely on homeopathy in human subjects for evidence of activity. It has been surprisingly discovered by the inventor of the present application and amply demonstrated in the accepted pharmacological models that the solvent ultimately obtained from consecutive multiple dilution of a starting molecular form of an antibody has definitive activity unrelated to the presence of the traces of the molecular form of the antibody in the target dilution. The "activated-potentiated" form of the antibody provided herein are tested for biological activity in well accepted pharmacological models of activity, either in appropriate in vitro experiments, or in vivo in suitable animal models. The experiments provided further below provide evidence of biological activity in such models. The human clinical studies, also provided herein below, inter alia provide evidence that the activity observed in the animal model is well translated to human therapy. The human study also provides evidence of availability of the "activated potentiated" forms described herein to treat specified human diseases or disorders well accepted as pathological conditions in the medical science.

Also, the claimed "activated-potentiated" form of antibody encompasses only solutions or solid preparations the biological activity of which cannot be explained by the presence of the molecular form of the antibody remaining from the initial, starting solution. In other words, while it is contemplated that the "activated-potentiated" form of the antibody may contain traces of the initial molecular form of the antibody, one skilled in the art could not attribute the observed biological activity in the accepted pharmacological models to the remaining molecular form of the antibody with any degree of plausibility due to the extremely low concentrations of the molecular form of the antibody remaining after the consecutive dilutions.

While the invention is not limited by any specific theory, the biological activity of the "activated-potentiated' form of the antibodies of the present invention is not attributable to the initial molecular form of the antibody. Preferred is the "activated-potentiated" form of antibody in liquid or solid form in which the concentration of the initial molecular form of the antibody is below the limit of detection of the accepted analytical techniques, such as capillary electrophoresis and High Performance Liquid Chromatography. Particularly preferred is the "activated-potentiated" form of antibody in liquid or solid form in which the concentration of the initial molecular form of the antibody is below the Avogadro number. In pharmacology of molecular forms of therapeutic substances, it is common practice to create a dose-response curve in which the level of pharmacological response is plotted against the concentration of the active drug administered to the subject or tested in vitro. The minimal level of the drug which produces any detectable response is known as a threshold dose. It is specifically contemplated and preferred that the "activated-potentiated" form of the antibodies contains molecular antibody, if any, at a concentration below the threshold dose for the molecular form of the antibody in the given biological model. The specific compositions described in the appended examples are described with the term ultra-low doses (ULD), which term is not intended to be used in construing the claims of the present application.

The term "cardiovascular condition" denotes disease or disorder of the cardiovascular system in human defined as such in the medical profession. Non-limiting examples of cardiovascular conditions include heart failure, arterial hypertension, and asthenia.

The term "symptom" with respect to "cardiovascular conditions" denotes those manifestations of patients suffering from diseases or disorders of the cardiovascular system that reduce quality of life of such patients. Non-limiting examples of symptoms of cardiovascular conditions that reduce quality of life include anxiety, depression, and walking difficulty.

The term "quality of life" denotes the subjective feeling of well-being of a patient. The quality of life of a patient increases with reduction in or improvement of symptoms. The term "quality of life" is meant to define the collection of symptoms associated with cardiovascular deceases or disorders in a patient population.

The term "MFI-20 scale" refers to "multidimensional fatigue inventory", which is a 20-question inventory questionnaire used to measure the levels of physical, psychological and mental fatigue. It denotes the MFI-20 questionnaire commonly used by those skilled in the art. An example of use of the MFI-20 scale to assess fatigue in patients with chronic heart failure may be found in K. Falk et al., Fatigue and Anaemia in Patients with Chronic Heart Failure, European Journal of Heart Failure, 8, 744-749 (2006), which is incorporated herein by reference.

The term "The Minnesota Living with Heart Failure questionnaire" (MLHFQ), also referred to as the Minnesota questionnaire, refers to a well-established questionnaire commonly used to assess quality of life and levels of anxiety in people with cardiovascular conditions, and heart failure in particular.

The content of the Minnesota questionnaire is representative of the ways cardiovascular conditions, and particularly heart failure, together with appropriate treatments, affect the physical, emotional, social and mental dimensions of quality of life. The questionnaire focuses on questions that assess the impact of frequent physical symptoms - shortness of breath, fatigue, peripheral edema, and sleeping difficulty, and psychological symptoms of anxiety and depression. In addition, the effects of heart failure on physical/social functions including walking, climbing stairs, household work, need to rest, working to earn a living, going places away from home, doing things with family or friends, recreational activities, sexual activities, eating and mental and emotional functions of concentration, memory, loss of self-control, and being a burden to others were incorporated into the measure. Since treatments might have side effects in addition to ameliorating symptoms and functional limitations produced by heart failure, questions about side effects of medications, hospital stays and costs of care are included to help measure the overall impact of a treatment on quality of life. To measure the effects of symptoms, functional limitations, psychological distress on an individual's quality of life, the questionnaire asks each person to indicate using a 6-point, zero to five, Likert scale how much each of 21 facets prevented them from living as they desired. This response format is consistent with the concept of quality of life and allows each individual to weigh each item using a common scale. Therefore, one can look at which items had the most effect and the sum of responses reflects the overall effects

of heart failure and treatments on the individual's quality of life. Although the Minnesota Living with Heart Failure Questionnaire incorporates relevant aspects of the key dimensions of quality of life, the questionnaire was not designed to measure any particular dimension separately. Given the conceptual basis for the questionnaire, items on the questionnaire are considered to be 'causal' indicators of quality of life in the sense that they can affect someone's quality of life when they occur, but may not be present when other aspects of heart failure are affecting an individual's quality of life. The total score is taken as the best measure of how cardiovascular condition, and particularly heart failure, and commensurate treatments impact the quality of life.

The term "Kansas City Cardiomyopathy Questionnaire" (KCCQ) or "Kansas Questionnaire" refers to a health-related quality-of-life measure for patients with congestive heart failure. It is a reliable, predictive tool that tracks how patients are doing if they have weakened heart muscle due to prior heart attacks, heart valve problems, viral infections, or other causes.

The answers patients give to the KCCQ's questions are used to calculate scores in ten scales:

1. **Physical Limitation**: a measure of how much a patient's condition is hampering his ability to do what he wants to do
2. **Symptom Stability**: a measure of whether a patient's symptoms are changing over time
3. **Symptom Frequency**: a measure of how often a patient has symptoms
4. **Symptom Burden**: a measure of what the impact of these symptoms are on the patient's well-being
5. **Total Symptom**: a combined measure of the symptom scales
6. **Social Limitation**: a measure of how much a patient's interpersonal relations are impacted by her condition
7. **Self-Efficacy**: a measure of how well a patient can manage her care, find answers and help
8. **Quality of Life**: a measure of the overall impact of a patient's condition on a patient's interpersonal relationships and state of mind

9. **Clinical Summary**: a combined measure of symptoms and social factors

10. **Overall Summary**: a combined measure of all the above

The term "Spielberg test" refers to the state-trait anxiety inventory for adults developed by Charles D. Spielberg which is well-accepted for measuring different forms of anxiety. The sampler manuals for performing the Spielberg test are published by Mind Gardens, Inc.

The term "Beck Questionnaire Score" refers to a score obtained from the Beck Depression Inventory, a widely used method for measuring depression developed by Aaron Beck. The description of a modern Beck Questionnaire may be found for example in Beck AT, Steer RA, Ball R, Ranieri W (December 1996). "*Comparison of Beck Depression Inventories -IA and -II in psychiatric outpatients*". Journal of personality assessment 67 (3): 588–97, incorporated herein by reference.

The term "in reference to the baseline" with respect to the score obtained from patient questionnaires denotes a comparison to the pre-treatment score of the same patient population.

The present invention provides a pharmaceutical composition for administration to a patient suffering from at least one symptom of a cardiovascular condition associated with a reduced quality of life of the patient, the composition comprising a) an activated-potentiated form of an antibody to the C-terminal fragment of angiotensin II AT1 receptor, and b) an activated-potentiated form of an antibody to endothelial NO-synthase, wherein the administration of the pharmaceutical composition improves quality of life of the patient. As set forth herein above, each of the individual components of the combination is generally known for its own individual medical uses. However, the inventors of the present patent application surprisingly discovered that administration of the combination markedly improves the quality of life of patients with cardiovascular conditions, such as heart failure, asthenia, dystonia, and hypertension.

The pharmaceutical composition in accordance with this aspect of the invention may be in the liquid form or in solid form. Each of the activated potentiated forms of the antibodies included in the pharmaceutical composition is prepared from an initial molecular form of the antibody via a process accepted in homeopathic art.

The starting antibodies may be monoclonal, or polyclonal antibodies prepared in accordance with known processes, for example, as described in Immunotechniques, G. Frimel, M., "Meditsyna", 1987, p. 9-33; "Hum. Antibodies. Monoclonal and recombinant antibodies, 30 years after" by Laffly E., Sodoyer R. – 2005 – Vol. 14. – N 1-2. P.33-55, both incorporated herein by reference.

Monoclonal antibodies may be obtained, e.g., by means of hybridoma technology. The initial stage of the process includes immunization based on the principles already developed in the course of polyclonal antisera preparation. Further stages of work involve the production of hybrid cells generating clones of antibodies with identical specificity. Their separate isolation is performed using the same methods as in the case of polyclonal antisera preparation.

Polyclonal antibodies may be obtained via active immunization of animals. For this purpose, for example, suitable animals (e.g. rabbits) receive a series of injections of the appropriate antigen, either endothelial NO-synthase or angiotensin II AT1-receptor. The animals' immune system generates corresponding antibodies which are collected from the animals in a known manner. This procedure enables preparation of a monospecific antibody-rich serum. If desired, the serum containing antibodies may be purified, e.g. using affine chromatography, fractionation by salt precipitation, or ion-exchange chromatography. The resulting purified, antibody-enriched serum may be used as a starting material for preparation of the activated-potentiated form of the antibodies. The preferred concentration of the resulting initial solution of antibody in the solvent, preferably, water or a water-ethyl alcohol mixture, ranges from about 0.5 to about 5.0 mg/ml.

The preferred procedure for preparing each component of the combination drug according to the present invention is the use of the mixture of three aqueous-alcohol dilutions of the primary matrix solution of antibodies diluted 100^{12}, 100^{30} and 100^{200} times, respectively, which is equivalent to centesimal homeopathic dilutions C12, C30 and C200. To prepare a solid dosage form, a solid carrier is treated with the desired dilution obtained via the homeopathic process. To obtain a solid unit dosage form of the combination of the invention, the carrier mass is impregnated

with each of the dilutions. Both orders of impregnation are suitable to prepare the desired combination dosage form.

In a preferred embodiment, the starting material for the preparation of the activated potentiated form that comprise the combination of the invention is polyclonal, animal-raised antibody to the corresponding antigen, namely, the C-terminal fragment of angiotensin II AT1 receptor and endothelial NO- synthase. To obtain the activated-potentiated form of polyclonal antibodies to the C-terminal fragment of angiotensin II AT1 receptor, the desired antigen may be injected as immunogen into a laboratory animal, preferably, rabbits. The following sequences of the human angiotensin II AT1 receptor is specifically contemplated as suitable antigens. The use of a whole human angiotensin II AT1 receptor is specifically contemplated:

SEQ ID NO: 1

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Ser Pro Pro Ala Gly Thr Arg His Met Ala Asn Thr Tyr Pro Glu
 1               5                  10                  15
Ala Asn Gly Ile Thr Glu Asn Ser Ile Asn Ile Ile Arg Glu Cys
 16              20                  25                  30
Glu Pro Thr Arg Ser His Met Ser Ala Pro Ile Glu Asn Ser Gly
 31              35                  40                  45
Asn Ala Gly Thr Arg Pro Glu Ser Val Met Ile Leu Asn Ser Ser
 46              50                  55                  60
Thr Glu Asp Gly Ile Lys Arg Ile Gln Asp Asp Cys Pro Lys Ala
 61              65                  70                  75
Gly Arg His Asn Tyr Ile Phe Val Met Ile Pro Thr Leu Tyr Ser
 76              80                  85                  90
Ile Ile Phe Val Val Gly Ile Phe Gly Asn Ser Leu Val Val Ile
 91              95                 100                 105
Val Ile Tyr Phe Tyr Met Lys Leu Lys Thr Val Ala Ser Val Phe
106             110                 115                 120
Leu Leu Asn Leu Ala Leu Ala Asp Leu Cys Phe Leu Leu Thr Leu
121             125                 130                 135
Pro Leu Trp Ala Val Tyr Thr Ala Met Glu Tyr Arg Trp Pro Phe
136             140                 145                 150
Gly Asn Tyr Leu Cys Lys Ile Ala Ser Ala Ser Val Ser Phe Asn
151             155                 160                 165
Leu Tyr Ala Ser Val Phe Leu Leu Thr Cys Leu Ser Ile Asp Arg
166             170                 175                 180
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Tyr Leu Ala Ile Val His Pro Met Lys Ser Arg Leu Arg Arg Thr
181             185                 190                 195
Met Leu Val Ala Lys Val Thr Cys Ile Ile Ile Trp Leu Leu Ala
196             200                 205                 210
Gly Leu Ala Ser Leu Pro Ala Ile Ile His Arg Asn Val Phe Phe
211             215                 220                 225
Ile Glu Asn Thr Asn Ile Thr Val Cys Ala Phe His Tyr Glu Ser
226             230                 235                 240
Gln Asn Ser Thr Leu Pro Ile Gly Leu Gly Leu Thr Lys Asn Ile
241             245                 250                 255
Leu Gly Phe Leu Phe Pro Phe Leu Ile Ile Leu Thr Ser Tyr Thr
256             260                 265                 270
Leu Ile Trp Lys Ala Leu Lys Lys Ala Tyr Glu Ile Gln Lys Asn
271             275                 280                 285
Lys Pro Arg Asn Asp Asp Ile Phe Lys Ile Ile Met Ala Ile Val
286             290                 295                 300
Leu Phe Phe Phe Phe Ser Trp Ile Pro His Gln Ile Phe Thr Phe
301             305                 310                 315
Leu Asp Val Leu Ile Gln Leu Gly Ile Ile Arg Asp Cys Arg Ile
316             320                 325                 330
Ala Asp Ile Val Asp Thr Ala Met Pro Ile Thr Ile Cys Ile Ala
331             335                 340                 345
Tyr Phe Asn Asn Cys Leu Asn Pro Leu Phe Tyr Gly Phe Leu Gly
346             350                 355                 360
Lys Lys Phe Lys Arg Tyr Phe Leu Gln Leu Leu Lys Tyr Ile Pro
361             365                 370                 375
Pro Lys Ala Lys Ser His Ser Asn Leu Ser Thr Lys Met Ser Thr
376             380                 385                 390
Leu Ser Tyr Arg Pro Ser Asp Asn Val Ser Ser Ser Thr Lys Lys
391             395                 400                 405
Pro Ala Pro Cys Phe Glu Val Glu
406             410         413
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The use of different fragments of C-terminal fragment of human angiotensin II AT1 receptor with as antigen is also contemplated. The suitable sequences for such antigen are as follow:

SEQ ID NO: 2

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                                                        Gly
                                                        360
Lys Lys Phe Lys Arg Tyr Phe Leu Gln Leu Leu Lys Tyr Ile Pro
361             365                 370                 375
Pro Lys Ala Lys Ser His Ser Asn Leu Ser Thr Lys Met Ser Thr
376             380                 385                 390
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Leu Ser Tyr Arg Pro Ser Asp Asn Val Ser Ser Ser Thr Lys Lys
391             395                 400                 405
Pro Ala Pro Cys Phe Glu Val Glu
406             410         413
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SEQ ID NO: 3

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                                Gln Leu Leu Lys Tyr Ile Pro
                                369 370                 375
Pro Lys Ala
376     378
```

SEQ ID NO: 4

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                        Ser Asn Leu Ser Thr Lys Met Ser Thr
                        382         385                 390
Leu Ser Tyr Arg Pro Ser Asp Asn Val Ser Ser Ser Thr Lys Lys
391             395                 400                 405
Pro Ala Pro Cys Phe
406             410
```

The use of the fragments of C-terminal fragment of human angiotensin II AT1 receptor with N-terminal cysteine (Cys) as antigen is also contemplated. The suitable sequence for such antigen is as follow:

SEQ ID NO: 5

```
                                                    Cys Gly
                                                        360
Lys Lys Phe Lys Arg Tyr Phe Leu Gln Leu Leu Lys Tyr Ile Pro
361             365                 370                 375
Pro Lys Ala Lys Ser His Ser Asn Leu Ser Thr Lys Met Ser Thr
376             380                 385                 390
Leu Ser Tyr Arg Pro Ser Asp Asn Val Ser Ser Ser Thr Lys Lys
391             395                 400                 405
Pro Ala Pro Cys Phe Glu Val Glu
406             410         413
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SEQ ID NO: 6

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                                Cys Gln Leu Leu Lys Tyr Ile Pro
                                    369 370                 375
Pro Lys Ala
376     378
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SEQ ID NO: 7

```
                                Cys Ser Asn Leu Ser Thr Lys Met Ser Thr
                                    382         385                 390
Leu Ser Tyr Arg Pro Ser Asp Asn Val Ser Ser Ser Thr Lys Lys
391             395                 400                 405
Pro Ala Pro Cys Phe
406             410
```

The exemplary procedure for preparation of the starting polyclonal antibodies to C-terminal fragment of human angiotensin II AT1 receptor may be described as follows. In 7-9 days before blood sampling, 1-3 intravenous injections of the desired antigen are made to the rabbits to increase the level of polyclonal antibodies in the rabbit blood stream. Upon immunization, blood samples are taken to test the antibody level. Typically, the maximum level of immune reaction of the soluble antigen is achieved within 40 to 60 days after the first injection of the antigen. Upon completion of the first immunization cycle, rabbits have a 30-day rehabilitation period, after which re-immunization is performed with another 1-3 intravenous injections.

To obtain antiserum containing the desired antibodies, the immunized rabbits' blood is collected from rabbits and placed in a 50ml centrifuge tube. Product clots formed on the tube sides are removed with a wooden spatula, and a rod is placed into the clot in the tube center. The blood is then placed in a refrigerator for one night at the temperature of about 40°C. On the following day, the clot on the spatula is removed, and the remaining liquid is centrifuged for 10 min at 13,000 rpm. Supernatant fluid is the target antiserum. The obtained antiserum is typically yellow. 20% of NaN_3 (weight concentration) is added in the antiserum to a final concentration of 0.02% and stored before use in frozen state at the temperature of -20°C or without NaN_3 at the temperature of -70°C. To separate the target antibodies to the C-terminal fragment of angiotensin II AT1 receptor from the antiserum, the following solid phase absorption sequence is suitable:

10 ml of the antiserum of rabbits is diluted twofold with 0.15 M NaCl, after which 6.26g Na_2SO_4 is added, mixed and incubated for 12-16 hours at 4°C. The sediment is removed by centrifugation, diluted in 10ml of phosphate buffer and

dialyzed against the same buffer during one night at ambient temperature. After the sediment is removed, the solution is applied to a DEAE-cellulose column balanced by phosphate buffer. The antibody fraction is determined by measuring the optical density of eluate at 280 nm.

The isolated crude antibodies are purified using the affine chromatography method by attaching the obtained antibodies to a C-terminal fragment of angiotensin II AT1 receptor located on the insoluble matrix of the chromatography media, with subsequent elution by concentrated aqueous salt solutions.

The resulting buffer solution is used as the initial solution for the homeopathic dilution process used to prepare the activated potentiated form of the antibodies. The preferred concentration of the initial matrix solution of the antigen-purified polyclonal rabbit antibodies to a C-terminal fragment of angiotensin II AT1 receptor is 0.5 - 5.0 mg/ml, preferably, 2.0 - 3.0 mg/ml.

The polyclonal antibodies to endothelial NO-synthase are obtained by a similar methodology using an adjuvant. Preferably, the entire molecule of bovine endothelial NO-synthase is used as immunogen (antigen) for rabbits' immunization:

SEQ.ID. NO. 8

```
Met Gly Asn Leu Lys Ser Val Gly Gln Glu Pro Gly Pro Pro Cys
 1               5                  10                  15
Gly Leu Gly Leu Gly Leu Gly Leu Gly Leu Cys Gly Lys Gln Gly
 16              20                  25                  30
Pro Ala Ser Pro Ala Pro Glu Pro Ser Arg Ala Pro Ala Pro Ala
 31              35                  40                  45
Thr Pro His Ala Pro Asp His Ser Pro Ala Pro Asn Ser Pro Thr
 46              50                  55                  60
Leu Thr Arg Pro Pro Glu Gly Pro Lys Phe Pro Arg Val Lys Asn
 61              65                  70                  75
Trp Glu Leu GLys er Ile Thr Tyr Asp Thr Leu Cys Ala Gln Ser
 76              80                  85                  90
Gln Gln Asp Gly Pro Cys Thr Pro Arg Cys Cys Leu GLys er Leu
 91              95                 100                 105
Val Leu Pro Arg Lys Leu Gln Thr Arg Pro Ser Pro Gly Pro Pro
106             110                 115                 120
Pro Ala Glu Gln Leu Leu Ser Gln Ala Arg Asp Phe Ile Asn Gln
121             125                 130                 135
Tyr Tyr Ser Ser Ile Lys Arg Ser GLys er Gln Ala His Glu Glu
136             140                 145                 150
```

Arg Leu Gln Glu Val Glu Ala Glu Val Ala Ser Thr Gly Thr Tyr
151 155 160 165
His Leu Arg Glu Ser Glu Leu Val Phe Gly Ala Lys Gln Ala Trp
166 170 175 180
Arg Asn Ala Pro Arg Cys Val Gly Arg Ile Gln Trp Gly Lys Leu
181 185 190 195
Gln Val Phe Asp Ala Arg Asp Cys Ser Ser Ala Gln Glu Met Phe
196 200 205 210
Thr Tyr Ile Cys Asn His Ile Lys Tyr Ala Thr Asn Arg Gly Asn
211 215 220 225
Leu Arg Ser Ala Ile Thr Val Phe Pro Gln Arg Ala Pro Gly Arg
226 230 235 240
Gly Asp Phe Arg Ile Trp Asn Ser Gln Leu Val Arg Tyr Ala Gly
241 245 250 255
Tyr Arg Gln Gln Asp GLys er Val Arg Gly Asp Pro Ala Asn Val
256 260 265 270
Glu Ile Thr Glu Leu Cys Ile Gln His Gly Trp Thr Pro Gly Asn
271 275 280 285
Gly Arg Phe Asp Val Leu Pro Leu Leu Leu Gln Ala Pro Asp Glu
286 290 295 300
Ala Pro Glu Leu Phe Val Leu Pro Pro Glu Leu Val Leu Glu Val
301 305 310 315
Pro Leu Glu His Pro Thr Leu Glu Trp Phe Ala Ala Leu Gly Leu
316 320 325 330
Arg Trp Tyr Ala Leu Pro Ala Val Ser Asn Met Leu Leu Glu Ile
331 335 340 345
Gly Gly Leu Glu Phe Ser Ala Ala Pro Phe Ser Gly Trp Tyr Met
346 350 355 360
Ser Thr Glu Ile Gly Thr Arg Asn Leu Cys Asp Pro His Arg Tyr
361 365 370 375
Asn Ile Leu Glu Asp Val Ala Val Cys Met Asp Leu Asp Thr Arg
376 380 385 390
Thr Thr Ser Ser Leu Trp Lys Asp Lys Ala Ala Val Glu Ile Asn
391 395 400 405
Leu Ala Val Leu His Ser Phe Gln Leu Ala Lys Val Thr Ile Val
406 410 415 420
Asp His His Ala Ala Thr Val Ser Phe Met Lys His Leu Asp Asn
421 425 430 435
Glu Gln Lys Ala Arg Gly Gly Cys Pro Ala Asp Trp Ala Trp Ile
436 440 445 450
Val Pro Pro Ile Ser GLys er Leu Thr Pro Val Phe His Gln Glu
451 455 460 465
Met Val Asn Tyr Ile Leu Ser Pro Ala Phe Arg Tyr Gln Pro Asp
466 470 475 480
Pro Trp Lys GLy Ser Ala Thr Lys Gly Ala Gly Ile Thr Arg Lys
481 485 490 495

Lys Thr Phe Lys Glu Val Ala Asn Ala Val Lys Ile Ser Ala Ser
496 500 505 510
Leu Met Gly Thr Leu Met Ala Lys Arg Val Lys Ala Thr Ile Leu
511 515 510 525
Tyr Ala Ser Glu Thr Gly Arg Ala Gln Ser Tyr Ala Gln Gln Leu
526 530 535 540
Gly Arg Leu Phe Arg Lys Ala Phe Asp Pro Arg Val Leu Cys Met
541 545 550 555
Asp Glu Tyr Asp Val Val Ser Leu Glu His Glu Ala Leu Val Leu
556 560 565 570
Val Val Thr Ser Thr Phe Gly Asn Gly Asp Pro Pro Glu Asn Gly
571 575 580 585
Glu Ser Phe Ala Ala Ala Leu Met Glu Met Ser Gly Pro Tyr Asn
586 590 595 600
Ser Ser Pro Arg Pro Glu Gln His Lys Ser Tyr Lys Ile Arg Phe
601 605 610 615
Asn Ser Val Ser Cys Ser Asp Pro Leu Val Ser Ser Trp Arg Arg
616 620 625 630
Lys Arg Lys Glu Ser Ser Asn Thr Asp Ser Ala Gly Ala Leu Gly
631 635 640 645
Thr Leu Arg Phe Cys Val Phe Gly Leu GLy Ser Arg Ala Tyr Pro
646 650 655 660
His Phe Cys Ala Phe Ala Arg Ala Val Asp Thr Arg Leu Glu Glu
661 665 670 675
Leu Gly Gly Glu Arg Leu Leu Gln Leu Gly Gln Gly Asp Glu Leu
676 680 685 690
Cys Gly Gln Glu Glu Ala Phe Arg Gly Trp Ala Lys Ala Ala Phe
691 695 700 705
Gln Ala Ser Cys Glu Thr Phe Cys Val Gly Glu Glu Ala Lys Ala
706 710 715 720
Ala Ala Gln Asp Ile Phe Ser Pro Lys Arg Ser Trp Lys Arg Gln
721 725 730 735
Arg Tyr Arg Leu Ser Thr Gln Ala Glu Gly Leu Gln Leu Leu Pro
736 740 745 750
Gly Leu Ile His Val His Arg Arg Lys Met Phe Gln Ala Thr Val
751 755 760 765
Leu Ser Val Glu Asn Leu Gln Ser Ser Lys Ser Thr Arg Ala Thr
766 770 775 780
Ile Leu Val Arg Leu Asp Thr Ala Gly Gln Glu Gly Leu Gln Tyr
781 785 790 795
Gln Pro Gly Asp His Ile Gly Ile Cys Pro Pro Asn Arg Pro Gly
796 800 805 810
Leu Val Glu Ala Leu Leu Ser Arg Val Glu Asp Pro Pro Pro Pro
811 815 820 825
Thr Glu Ser Val Ala Val Glu Gln Leu Glu Lys GLys er Pro Gly
826 830 835 840

```
Gly Pro Pro Pro Ser Trp Val Arg Asp Pro Arg Leu Pro Pro Cys
841             845                 850                 855
Thr Leu Arg Gln Ala Leu Thr Phe Phe Leu Asp Ile Thr Ser Pro
856             860                 865                 870
Pro Ser Pro Arg Leu Leu Arg Leu Leu Ser Thr Leu Ala Glu Glu
871             875                 880                 885
Pro Ser Glu Gln Gln Glu Leu Glu Thr Leu Ser Gln Asp Pro Arg
886             890                 895                 900
Arg Tyr Glu Glu Trp Lys Trp Phe Arg Cys Pro Thr Leu Leu Glu
901             905                 910                 915
Val Leu Glu Gln Phe Pro Ser Val Ala Leu Pro Ala Pro Leu Leu
916             920                 925                 930
Leu Thr Gln Leu Pro Leu Leu Gln Pro Arg Tyr Tyr Ser Val Ser
931             935                 940                 945
Ser Ala Pro Asn Ala His Pro Gly Glu Val His Leu Thr Val Ala
946             950                 955                 960
Val Leu Ala Tyr Arg Thr Gln Asp Gly Leu Gly Pro Leu His Tyr
961             965                 970                 975
Gly Val Cys Ser Thr Trp Leu Ser Gln Leu Lys Thr Gly Asp Pro
976             980                 985                 990
Val Pro Cys Phe Ile Arg Gly Ala Pro Ser Phe Arg Leu Pro Pro
991             995                1000                1005
Asp Pro Tyr Val Pro Cys Ile Leu Val Gly Pro Gly Thr Gly Ile
1006           1010                1015                1020
Ala Pro Phe Arg Gly Phe Trp Gln Glu Arg Leu His Asp Ile Glu
1021           1025                1030                1035
Ser Lys Gly Leu Gln Pro Ala Pro Met Thr Leu Val Phe Gly Cys
1036           1040                1045                1050
Arg Cys Ser Gln Leu Asp His Leu Tyr Arg Asp Glu Val Gln Asp
1051           1055                1060                1065
Ala Gln Glu Arg Gly Val Phe Gly Arg Val Leu Thr Ala Phe Ser
1066           1070                1075                1080
Arg Glu Pro Asp Ser Pro Lys Thr Tyr Val Gln Asp Ile Leu Arg
1081           1085                1090                1095
Thr Glu Leu Ala Ala Glu Val His Arg Val Leu Cys Leu Glu Arg
1096           1100                1105                1110
Gly His Met Phe Val Cys Gly Asp Val Thr Met Ala Thr Ser Val
1111           1115                1120                1125
Leu Gln Thr Val Gln Arg Ile Leu Ala Thr Glu Gly Asp Met Glu
1126           1130                1135                1140
Leu Asp Glu Ala Gly Asp Val Ile Gly Val Leu Arg Asp Gln Gln
1141           1145                1150                1155
Arg Tyr His Glu Asp Ile Phe Gly Leu Thr Leu Arg Thr Gln Glu
1156           1160                1165                1170
Val Thr Ser Arg Ile Arg Thr Gln Ser Phe Ser Leu Gln Glu Arg
1171           1175                1180                1185
```

```
His Leu Arg Gly Ala Val Pro Trp Ala Phe Asp Pro Pro Gly Pro
1186           1190                1195                1200
Asp Thr Pro Gly Pro
1201           1205
```

Polyclonal antibodies to endothelial NO synthase may be obtained using the whole molecule of human endothelial NO synthase of the following sequence:

SEQ ID NO: 9

```
Met Gly Asn Leu Lys Ser Val Ala Gln Glu Pro Gly Pro Pro Cys
 1              5                  10                  15
Gly Leu Gly Leu Gly Leu Gly Leu Gly Leu Cys Gly Lys Gln Gly
 16             20                  25                  30
Pro Ala Thr Pro Ala Pro Glu Pro Ser Arg Ala Pro Ala Ser Leu
 31             35                  40                  45
Leu Pro Pro Ala Pro Glu His Ser Pro Pro Ser Ser Pro Leu Thr
 46             50                  55                  60
Gln Pro Pro Glu Gly Pro Lys Phe Pro Arg Val Lys Asn Trp Glu
 61             65                  70                  75
Val GLys er Ile Thr Tyr Asp Thr Leu Ser Ala Gln Ala Gln Gln
 76             80                  85                  90
Asp Gly Pro Cys Thr Pro Arg Arg Cys Leu GLys er Leu Val Phe
 91             95                 100                 105
Pro Arg Lys Leu Gln Gly Arg Pro Ser Pro Gly Pro Pro Ala Pro
106            110                 115                 120
Glu Gln Leu Leu Ser Gln Ala Arg Asp Phe Ile Asn Gln Tyr Tyr
121            125                 130                 135
Ser Ser Ile Lys Arg Ser GLys er Gln Ala His Glu Gln Arg Leu
136            140                 145                 150
Gln Glu Val Glu Ala Glu Val Ala Ala Thr Gly Thr Tyr Gln Leu
151            155                 160                 165
Arg Glu Ser Glu Leu Val Phe Gly Ala Lys Gln Ala Trp Arg Asn
166            170                 175                 180
Ala Pro Arg Cys Val Gly Arg Ile Gln Trp Gly Lys Leu Gln Val
181            185                 190                 195
Phe Asp Ala Arg Asp Cys Arg Ser Ala Gln Glu Met Phe Thr Tyr
196            200                 205                 210
Ile Cys Asn His Ile Lys Tyr Ala Thr Asn Arg Gly Asn Leu Arg
211            215                 220                 225
Ser Ala Ile Thr Val Phe Pro Gln Arg Cys Pro Gly Arg Gly Asp
226            230                 235                 240
Phe Arg Ile Trp Asn Ser Gln Leu Val Arg Tyr Ala Gly Tyr Arg
241            245                 250                 255
Gln Gln Asp GLy Ser Val Arg Gly Asp Pro Ala Asn Val Glu Ile
```

256 260 265 270
Thr Glu Leu Cys Ile Gln His Gly Trp Thr Pro Gly Asn Gly Arg
271 275 280 285
Phe Asp Val Leu Pro Leu Leu Leu Gln Ala Pro Asp Glu Pro Pro
286 290 295 300
Glu Leu Phe Leu Leu Pro Pro Glu Leu Val Leu Glu Val Pro Leu
301 305 310 315
Glu His Pro Thr Leu Glu Trp Phe Ala Ala Leu Gly Leu Arg Trp
316 320 325 330
Tyr Ala Leu Pro Ala Val Ser Asn Met Leu Leu Glu Ile Gly Gly
331 335 340 345
Leu Glu Phe Pro Ala Ala Pro Phe Ser Gly Trp Tyr Met Ser Thr
346 350 355 360
Glu Ile Gly Thr Arg Asn Leu Cys Asp Pro His Arg Tyr Asn Ile
361 365 370 375
Leu Glu Asp Val Ala Val Cys Met Asp Leu Asp Thr Arg Thr Thr
376 380 385 390
Ser Ser Leu Trp Lys Asp Lys Ala Ala Val Glu Ile Asn Val Ala
391 395 400 405
Val Leu His Ser Tyr Gln Leu Ala Lys Val Thr Ile Val Asp His
406 410 415 420
His Ala Ala Thr Ala Ser Phe Met Lys His Leu Glu Asn Glu Gln
421 425 430 435
Lys Ala Arg Gly Gly Cys Pro Ala Asp Trp Ala Trp Ile Val Pro
436 440 445 450
Pro Ile Ser GLys er Leu Thr Pro Val Phe His Gln Glu Met Val
451 455 460 465
Asn Tyr Phe Leu Ser Pro Ala Phe Arg Tyr Gln Pro Asp Pro Trp
466 470 475 480
Lys GLys er Ala Ala Lys Gly Thr Gly Ile Thr Arg Lys Lys Thr
481 485 490 495
Phe Lys Glu Val Ala Asn Ala Val Lys Ile Ser Ala Ser Leu Met
496 500 505 510
Gly Thr Val Met Ala Lys Arg Val Lys Ala Thr Ile Leu Tyr Gly
511 515 510 525
Ser Glu Thr Gly Arg Ala Gln Ser Tyr Ala Gln Gln Leu Gly Arg
526 530 535 540
Leu Phe Arg Lys Ala Phe Asp Pro Arg Val Leu Cys Met Asp Glu
541 545 550 555
Tyr Asp Val Val Ser Leu Glu His Glu Thr Leu Val Leu Val Val
556 560 565 570
Thr Ser Thr Phe Gly Asn Gly Asp Pro Pro Glu Asn Gly Glu Ser
571 575 580 585
Phe Ala Ala Ala Leu Met Glu Met Ser Gly Pro Tyr Asn Ser Ser
586 590 595 600
Pro Arg Pro Glu Gln His Lys Ser Tyr Lys Ile Arg Phe Asn Ser

601 605 610 615
Ile Ser Cys Ser Asp Pro Leu Val Ser Ser Trp Arg Arg Lys Arg
616 620 625 630
Lys Glu Ser Ser Asn Thr Asp Ser Ala Gly Ala Leu Gly Thr Leu
631 635 640 645
Arg Phe Cys Val Phe Gly Leu GLys er Arg Ala Tyr Pro His Phe
646 650 655 660
Cys Ala Phe Ala Arg Ala Val Asp Thr Arg Leu Glu Glu Leu Gly
661 665 670 675
Gly Glu Arg Leu Leu Gln Leu Gly Gln Gly Asp Glu Leu Cys Gly
676 680 685 690
Gln Glu Glu Ala Phe Arg Gly Trp Ala Gln Ala Ala Phe Gln Ala
691 695 700 705
Ala Cys Glu Thr Phe Cys Val Gly Glu Asp Ala Lys Ala Ala Ala
706 710 715 720
Arg Asp Ile Phe Ser Pro Lys Arg Ser Trp Lys Arg Gln Arg Tyr
721 725 730 735
Arg Leu Ser Ala Gln Ala Glu Gly Leu Gln Leu Leu Pro Gly Leu
736 740 745 750
Ile His Val His Arg Arg Lys Met Phe Gln Ala Thr Ile Arg Ser
751 755 760 765
Val Glu Asn Leu Gln Ser Ser Lys Ser Thr Arg Ala Thr Ile Leu
766 770 775 780
Val Arg Leu Asp Thr Gly Gly Gln Glu Gly Leu Gln Tyr Gln Pro
781 785 790 795
Gly Asp His Ile Gly Val Cys Pro Pro Asn Arg Pro Gly Leu Val
796 800 805 810
Glu Ala Leu Leu Ser Arg Val Glu Asp Pro Pro Ala Pro Thr Glu
811 815 820 825
Pro Val Ala Val Glu Gln Leu Glu Lys Gly Ser Pro Gly Gly Pro
826 830 835 840
Pro Pro Gly Trp Val Arg Asp Pro Arg Leu Pro Pro Cys Thr Leu
841 845 850 855
Arg Gln Ala Leu Thr Phe Phe Leu Asp Ile Thr Ser Pro Pro Ser
856 860 865 870
Pro Gln Leu Leu Arg Leu Leu Ser Thr Leu Ala Glu Glu Pro Arg
871 875 880 885
Glu Gln Gln Glu Leu Glu Ala Leu Ser Gln Asp Pro Arg Arg Tyr
886 890 895 900
Glu Glu Trp Lys Trp Phe Arg Cys Pro Thr Leu Leu Glu Val Leu
901 905 910 915
Glu Gln Phe Pro Ser Val Ala Leu Pro Ala Pro Leu Leu Leu Thr
916 920 925 930
Gln Leu Pro Leu Leu Gln Pro Arg Tyr Tyr Ser Val Ser Ser Ala
931 935 940 945
Pro Ser Thr His Pro Gly Glu Ile His Leu Thr Val Ala Val Leu

946 950 955 960
Ala Tyr Arg Thr Gln Asp Gly Leu Gly Pro Leu His Tyr Gly Val
961 965 970 975
Cys Ser Thr Trp Leu Ser Gln Leu Lys Pro Gly Asp Pro Val Pro
976 980 985 990
Cys Phe Ile Arg Gly Ala Pro Ser Phe Arg Leu Pro Pro Asp Pro
991 995 1000 1005
Ser Leu Pro Cys Ile Leu Val Gly Pro Gly Thr Gly Ile Ala Pro
1006 1010 1015 1020
Phe Arg Gly Phe Trp Gln Glu Arg Leu His Asp Ile Glu Ser Lys
1021 1025 1030 1035
Gly Leu Gln Pro Thr Pro Met Thr Leu Val Phe Gly Cys Arg Cys
1036 1040 1045 1050
Ser Gln Leu Asp His Leu Tyr Arg Asp Glu Val Gln Asn Ala Gln
1051 1055 1060 1065
Gln Arg Gly Val Phe Gly Arg Val Leu Thr Ala Phe Ser Arg Glu
1066 1070 1075 1080
Pro Asp Asn Pro Lys Thr Tyr Val Gln Asp Ile Leu Arg Thr Glu
1081 1085 1090 1095
Leu Ala Ala Glu Val His Arg Val Leu Cys Leu Glu Arg Gly His
1096 1100 1105 1110
Met Phe Val Cys Gly Asp Val Thr Met Ala Thr Asn Val Leu Gln
1111 1115 1120 1125
Thr Val Gln Arg Ile Leu Ala Thr Glu Gly Asp Met Glu Leu Asp
1126 1130 1135 1140
Glu Ala Gly Asp Val Ile Gly Val Leu Arg Asp Gln Gln Arg Tyr
1141 1145 1150 1155
His Glu Asp Ile Phe Gly Leu Thr Leu Arg Thr Gln Glu Val Thr
1156 1160 1165 1170
Ser Arg Ile Arg Thr Gln Ser Phe Ser Leu Gln Glu Arg Gln Leu
1171 1175 1180 1185
Arg Gly Ala Val Pro Trp Ala Phe Asp Pro Pro Gly Ser Asp Thr
1186 1190 1195 1200
Asn Ser Pro
1201 1203

To obtain polyclonal antibodies to endothelial NO synthase, it is also possible to use a fragment of endothelial NO synthase, selected, for example, from the following sequences:

SEQ ID NO: 10

```
Pro Trp Ala Phe
1192       1195
```

SEQ ID NO: 11

```
Gly Ala Val Pro
1189       1192
```

SEQ ID NO: 12

```
                                                              Arg
                                                             1185
His Leu Arg Gly Ala Val Pro Trp Ala Phe Asp Pro Pro Gly Pro
1186           1190                1195                1200
Asp Thr Pro Gly Pro
1201           1205
```

SEQ. ID. NO. 13

```
                                  Ala Phe Asp Pro Pro Gly Pro
                                  11941195                1200
Asp Thr Pro Gly Pro
1201           1205
```

SEQ. NO. 14

```
His Leu Arg Gly Ala Val Pro Trp Ala Phe Asp
1186           1190                11951196
```

SEQ ID NO: 15

```
His Leu Arg Gly Ala Val Pro Trp Ala Phe Asp Pro Pro Gly Pro
1186           1190                1195                1200
Asp Thr Pro Gly Pro
1201           1205
```

The activated potentiated form of each component of the combination may be prepared from an initial solution by homeopathic potentization, preferably using the

method of proportional concentration decrease by serial dilution of 1 part of each preceding solution (beginning with the initial solution) in 9 parts (for decimal dilution), or in 99 parts (for centesimal dilution), or in 999 parts (for millesimal dilution) of a neutral solvent, starting with a concentration of the initial solution of antibody in the solvent, preferably, water or a water-ethyl alcohol mixture, in the range from about 0.5 to about 5.0 mg/ml, coupled with external impact. Preferably, the external impact involves multiple vertical shaking (dynamization) of each dilution. Preferably, separate containers are used for each subsequent dilution up to the required potency level, or the dilution factor. This method is well-accepted in the homeopathic art. See, e.g. V. Schwabe "Homeopathic medicines", M., 1967, p. 14-29, incorporated herein by reference for the purpose stated.

For example, to prepare a 12-centesimal dilution (denoted C12), one part of the initial matrix solution of antibodies, for example, to C-terminal fragment of angiotensin II AT1 receptor with the concentration of 3.0 mg/ml is diluted in 99 parts of neutral aqueous or aqueous-alcohol solvent (preferably, 15%-ethyl alcohol) and then vertically shaked many times (10 and more) to create the 1st centesimal dilution (denoted as C1). The 2nd centesimal dilution (C2) is prepared from the 1st centesimal dilution C1. This procedure is repeated 11 times to prepare the 12th centesimal dilution C12. Thus, the 12th centesimal dilution C12 represents a solution obtained by 12 serial dilutions of one part of the initial matrix solution of antibodies to C-terminal fragment of angiotensin II AT1 receptor with the concentration of 3.0 mg/ml in 99 parts of a neutral solvent in different containers, which is equivalent to the centesimal homeopathic dilution C12. Similar procedures with the relevant dilution factor are performed to obtain dilutions C30 and C 200.The intermediate dilutions may be tested in a desired biological model to check activity. The preferred activated potentiated forms for both antibodies comprising the combination of the invention are a mixture of C12, C30, and C200 dilutions. When using the mixture of various homeopathic dilutions (primarily centesimal) of the active substance as biologically active liquid component, each component of the composition (e.g., C12, C30, C200) is prepared separately according to the above-described procedure until

the next-to-last dilution is obtained (e.g., until C11, C29, and C199 respectively), and then one part of each component is added in one container according to the mixture composition and mixed with the required quantity of the solvent (e.g. with 97 parts for centesimal dilution).

It is possible to use the active substance as mixture of various homeopathic dilutions, e.g. decimal and/or centesimal (D20, C30, C100 or C12, C30, C50 etc.), the efficiency of which is determined experimentally by testing the dilution in a suitable biological model, for example, in models described in the examples herein.

In the course of potentiation and concentration decrease, the vertical shaking may be substituted for external exposure to ultrasound, electromagnetic field or any similar external impact procedure accepted in the homeopathic art.

Preferably, the pharmaceutical composition of the invention may be in the form of a liquid or in the solid unit dosage form. The preferred liquid form of the pharmaceutical composition is a mixture, preferably at a 1:1 ratio of the activated potentiated form of antibodies to a C-terminal fragment of angiotensin II AT1 receptor and the activated potentiated form of antibodies to endothelial NO-synthase. The preferred liquid carrier is water or a water-ethyl alcohol mixture.

The solid unit dosage form of the pharmaceutical composition of the invention may be prepared by impregnating a solid, pharmaceutically acceptable carrier with the mixture of the activated potentiated form aqueous or aqueous-alcohol solutions of active components which are mixed, primarily in 1:1 ratio and used in liquid dosage form. Alternatively, the carrier may be impregnated consecutively with each requisite dilution. Both orders of impregnation are acceptable.

Preferably, the pharmaceutical composition in the solid unit dosage form is prepared from granules of the pharmaceutically acceptable carrier which were previously saturated with the aqueous or aqueous-alcoholic dilutions of the activated potentiated form of antibodies to a C-terminal fragment of angiotensin II AT1 receptor and the activated potentiated form of antibodies to endothelial NO-synthase. The solid dosage form may be in any form known in the pharmaceutical art, including a tablet, a capsule, a lozenge, and others. As an inactive

pharmaceutical ingredients one can use glucose, sucrose, maltose, amylum, isomaltose, isomalt and other mono- olygo- and polysaccharides used in manufacturing of pharmaceuticals as well as technological mixtures of the above mentioned inactive pharmaceutical ingredients with other pharmaceutically acceptable excipients, for example isomalt, crospovidone, sodium cyclamate, sodium saccharine, anhydrous citric acid etc), including lubricants, disintegrants, binders and coloring agents. The preferred carriers are lactose and isomalt. The pharmaceutical dosage form may further include standard pharmaceutical excipients, for example, microcrystalline cellulose, magnesium stearate and citric acid.

The example of preparation of the solid unit dosage form is set forth below. To prepare the solid oral form, 100-300 μm granules of lactose are impregnated with aqueous or aqueous-alcoholic solutions of the activated-potentiated form of antibodies to C-terminal fragment of angiotensin II AT1 receptor and the activated-potentiated form of antibodies to endothelial NO-synthase in the ratio of 1 kg of antibody solution to 5 or 10 kg of lactose (1:5 - 1:10). To effect impregnation, the lactose granules are exposed to saturation irrigation in the fluidized boiling bed in the boiling bed plant (e.g. "Hüttlin Pilotlab" by Hüttlin GmbH) with subsequent drying via heated air flow at a temperature below 40°C. The estimated quantity of the dried granules (10 to 34 weight parts) saturated with the activated potentiated form of antibodies is placed in the mixer, and mixed with 25 to 45 weight parts of "non-saturated" pure lactose (used for the purposes of cost reduction and simplification and acceleration of the technological process without decreasing the treatment efficiency), together with 0.1 to 1 weight parts of magnesium stearate, and 3 to 10 weight parts of microcrystalline cellulose. The obtained tablet mass is uniformly mixed, and tableted by direct dry pressing (e.g., in a Korsch – XL 400 tablet press) to form 150 to 500 mg round pills, preferably, 300 mg. After tableting, 300 mg pills are obtained that are saturated with aqueous-alcohol solution (3.0-6.0 mg/pill) of the combination of the activated-potentiated form of antibodies to C-terminal fragment of angiotensin II AT1 receptor and the activated potentiated form of antibodies to

endothelial NO-synthase. Each component of the combination used to impregnate the carrier is in the form of a mixture of centesimal homeopathic dilutions, preferably, C12, C30 and C200. While the invention is not limited to any specific theory, it is believed that the activated potentiated form of the antibodies described herein do not contain the molecular form of the antibody in an amount sufficient to have biological activity attributed to such molecular form. The biological activity of the combination drug (combination pharmaceutical composition) of the invention is amply demonstrated in the appended examples.

The combination pharmaceutical composition of the invention may be used for administration to patients having any cardiovascular condition specifically for the purpose of improving the quality of life of such patients. Such use is particularly advantageous because the side effect profile of the combination of the invention is highly favorable. Patients with cardiovascular conditions suffer from decreased quality of life due to their symptoms and decrease in their ability to engage in routine tasks, such as walking, moving items in their environment, depression, and anxiety. As shown in the appended examples, the administration of the combination drug of the invention to such patients improves their overall quality of life, ability to walk, decreases anxiety and depression associated specifically with their primary condition of the cardiovascular system.

The population of patients suffering from cardiovascular conditions, such as, for example, chronic heart failure, asthenia, dystonia, hypertension, and others, is routinely prescribed a variety of medications to treat their conditions. The use of the combination drug of the invention with such additional therapeutic agents to improve the quality of life, to treat chronic heart failure, dystonia, asthenia, and hypertension is specifically contemplated. Non-limiting examples of suitable additional therapeutic agents include:

- ACE inhibitors, including combined ones (Enap, Enalapril, Capoten, Renitec, Prestarium (Berlipril, Diroton, Capoten, Quadropril, Monopril, Renitec, Prestarium, Noliprel-Forte, Enap-N));

- diuretics (Furosemide, Veroshpiron, Hypothiazid, Arifon Retard, Indapamide, Hypothiazid, Diuver, Indap, Indapamide);

- β-adrenergic blockers (Egilok, Atenolol, Concor, Betaloc ZOK);

- nitrates (Dilasidom, Kardiket, Kardiket-Retord, Mitrolinate, MonoMak, Monocinque, Nitroglycerin, Nitrosorbid, Olicard, Pectrol, Sydnopharm);

- cardiac glycosides (Digoxin);

- calcium antagonists (Normodipin, Cordaflex, Amlovas, Amlodipine, Amlovas, Amlotop, Cardilopin, Cordaflex, Cordipin XL);

- hypolipidemic agents (Vasilip, Liprimar, Liptonorm, Simvahexal, Simvastol, Simvacard, Simgal, Tulip);

- antiaggregants (Acetylsalicylic acid, CardiASK, Cardiomagnyl, Thrombo ASS);

- antihypoxants (Preductal MB, Preductal, Trimectal);

- *anticoagulants (Warfarin).*

Preferably, for the purpose of improving the quality of life, the combination drug of the invention is administered from once daily to four times daily, each administration including one or two combination unit dosage forms.

It is known that a variety of cardiovascular conditions is accompanied with anxiety and/or depression in the relevant population of patients. The administration of the combination drug described herein to such patients results in a statistically significant improvement in the levels of anxiety and/or depression as measured by the well-accepted tests described herein and exemplified in the examples.

The combination pharmaceutical composition of the invention is also useful for treating chronic heart failure, primarily at the 1st and 2nd stages of the disease. It has been demonstrated experimentally that the administration of the combination pharmaceutical composition of the invention to patients that suffer from chronic heart failure leads to statistically significant improvement in rigidity parameters of carotid radial artery segments and carotid femoral artery segments. The combination of the invention provides an unexpected synergistic therapeutic effect and enhanced influence on vascular remodeling and endothelium dysfunction that is significant for

the process and progression of treatment of chronic heart failure, as also on the improvement of the patients' life quality, on morphological parameters of the heart and tolerance to physical exercise, which is confirmed by clinical trials.

The administration of the combination pharmaceutical composition for treatment of patients with chronic heart failure improves the life quality parameters evaluated by such criteria as depression, anxiety, walking duration, increased tolerance to physical exercise, etc. The patients that suffer from chronic heart failure also often suffer from associated anxiety and/or depression. The administration of the combination pharmaceutical composition to patients that suffer from chronic heart failure leads to a statistically significant reduction in anxiety and depression associated with their primary condition. It has been demonstrated experimentally that the administration of the combination to patients with chronic heart failure leads to statistically significant improvement in The Minnesota Living with Heart Failure questionnaire Score, Kansas City Cardiomyopathy Questionnaire Total Score, HADS Total Score, and 6-minute walking test.

The population of patients suffering from chronic heart failure is routinely prescribed a variety of medications to treat their condition. The use of the combination drug of the invention with such additional therapeutic agents to improve the quality of life, to treat chronic heart failure, dystonia, asthenia, and hypertension is specifically contemplated. Non-limiting examples of suitable additional therapeutic agents include ACE inhibitors, including combined ones (Enap, Enalapril, Capoten, Renitec, Prestarium (Berlipril, Diroton, Capoten, Quadropril, Monopril, Renitec, Prestarium, Noliprel-Forte, Enap-N));

- diuretics (Furosemide, Veroshpiron, Hypothiazid, Arifon Retard, Indapamide, Hypothiazid, Diuver, Indap, Indapamide);

- β-adrenergic blockers (Egilok, Atenolol, Concor, Betaloc ZOK);

- nitrates (Dilasidom, Kardiket, Kardiket-Retord, Mitrolinate, MonoMak, Monocinque, Nitroglycerin, Nitrosorbid, Olicard, Pectrol, Sydnopharm);

- cardiac glycosides (Digoxin);

- calcium antagonists (Normodipin, Cordaflex, Amlovas, Amlodipine, Amlovas, Amlotop, Cardilopin, Cordaflex, Cordipin XL);

- hypolipidemic agents (Vasilip, Liprimar, Liptonorm, Simvahexal, Simvastol, Simvacard, Simgal, Tulip);

- antiaggregants (Acetylsalicylic acid, CardiASK, Cardiomagnyl, Thrombo ASS);

- antihypoxants (Preductal MB, Preductal, Trimectal);

- anticoagulants (Warfarin).

Particularly preferred are those additional therapeutic agents that are used in the medical art to treat chronic heart failure.

Preferably, for the purpose of treating chronic heart failure, the combination drug of the invention is administered from once daily to four times daily, each administration including one or two combination unit dosage forms. Each of the specific administration regiments within the described range is separately and specifically contemplated.

Separate administration of two independently prepared unit dosage forms, each containing one of the activated potentiated forms of antibodies of the combination is also contemplated.

The combination pharmaceutical composition of the invention is also useful for treating patients that suffer from asthenia and/or vegetative-vascular dystonia. It has been demonstrated experimentally that the administration of the combination pharmaceutical composition of the invention to patients that suffer from asthenia and/or vegetative-vascular dystonia leads to statistically significant improvement in rigidity parameters of carotid radial artery segments and carotid femoral artery segments. The combination pharmaceutical composition of the invention provides an unexpected synergistic therapeutic effect and enhanced influence on vascular remodeling and endothelium dysfunction that is significant for the process and progression of treatment of asthenia and/or vegetative-vascular dystonia, as also on the improvement of the patients' life quality, on morphological parameters of the heart and tolerance to physical exercise, which is confirmed by clinical trials.

The administration of the combination pharmaceutical composition for treatment of patients with asthenia and/or vegetative-vascular dystonia improves the life quality parameters evaluated by such criteria as depression, anxiety, walking duration, increased tolerance to physical exercise, etc. The patients that suffer from asthenia and/or vegetative-vascular dystonia also often suffer from associated anxiety and/or depression. The administration of the combination pharmaceutical composition to patients that suffer from asthenia and/or vegetative-vascular dystonia leads to a statistically significant reduction in anxiety and depression associated with their primary condition. It has been demonstrated experimentally that the administration of the combination pharmaceutical composition to patients with asthenia and/or vegetative-vascular dystonia leads to statistically significant reduction in MFI-20 scale score for mental asthenia and improvements in trait anxiety as measured by the Spielberg test.

The population of patients suffering from asthenia and/or vegetative-vascular dystonia is routinely prescribed a variety of medications to treat their condition. The use of the combination pharmaceutical composition of the invention with such additional therapeutic agents to improve the quality of life, to treat dystonia and asthenia is specifically contemplated. Non-limiting examples of suitable additional therapeutic agents include

- ACE inhibitors, including combined ones (Enap, Enalapril, Capoten, Renitec, Prestarium (Berlipril, Diroton, Capoten, Quadropril, Monopril, Renitec, Prestarium, Noliprel-Forte, Enap-N));

- diuretics (Furosemide, Veroshpiron, Hypothiazid, Arifon Retard, Indapamide, Hypothiazid, Diuver, Indap, Indapamide);

- β-adrenergic blockers (Egilok, Atenolol, Concor, Betaloc ZOK);

- nitrates (Dilasidom, Kardiket, Kardiket-Retord, Mitrolinate, MonoMak, Monocinque, Nitroglycerin, Nitrosorbid, Olicard, Pectrol, Sydnopharm);

- cardiac glycosides (Digoxin);

- calcium antagonists (Normodipin, Cordaflex, Amlovas, Amlodipine, Amlovas, Amlotop, Cardilopin, Cordaflex, Cordipin XL);

- hypolipidemic agents (Vasilip, Liprimar, Liptonorm, Simvahexal, Simvastol, Simvacard, Simgal, Tulip);

- antiaggregants (Acetylsalicylic acid, CardiASK, Cardiomagnyl, Thrombo ASS);

- antihypoxants (Preductal MB, Preductal, Trimectal);

- anticoagulants (Warfarin).

Particularly preferred are those additional therapeutic agents that are used in the medical art to treat asthenia and/or vegetative-vascular dystonia.

Preferably, for the purpose of treating asthenia and/or vegetative-vascular dystonia, the combination pharmaceutical composition of the invention is administered from once daily to four times daily, each administration including one or two combination unit dosage forms. Each of the specific administration regimens within the described range is separately and specifically contemplated. Separate administration of two independently prepared unit dosage forms, each containing one of the activated potentiated forms of antibodies of the combination drug is also contemplated.

The combination pharmaceutical composition of the invention is also useful for treating hypertension. It has been demonstrated experimentally that the administration of the combination pharmaceutical composition leads to statistically significant reduction in systolic blood pressure. The population of patients suffering from hypertension is routinely prescribed a variety of medications to treat their condition. The use of the combination pharmaceutical composition of the invention with such additional therapeutic agents to treat hypertension is specifically contemplated. Non-limiting examples of suitable additional therapeutic agents include

- ACE inhibitors, including combined ones (Enap, Enalapril, Capoten, Renitec, Prestarium (Berlipril, Diroton, Capoten, Quadropril, Monopril, Renitec, Prestarium, Noliprel-Forte, Enap-N));

- diuretics (Furosemide, Veroshpiron, Hypothiazid, Arifon Retard, Indapamide, Hypothiazid, Diuver, Indap, Indapamide);

- β-adrenergic blockers (Egilok, Atenolol, Concor, Betaloc ZOK);

- nitrates (Dilasidom, Kardiket, Kardiket-Retord, Mitrolinate, MonoMak, Monocinque, Nitroglycerin, Nitrosorbid, Olicard, Pectrol, Sydnopharm);

- cardiac glycosides (Digoxin);

- calcium antagonists (Normodipin, Cordaflex, Amlovas, Amlodipine, Amlovas, Amlotop, Cardilopin, Cordaflex, Cordipin XL);

- hypolipidemic agents (Vasilip, Liprimar, Liptonorm, Simvahexal, Simvastol, Simvacard, Simgal, Tulip);

- antiaggregants (Acetylsalicylic acid, CardiASK, Cardiomagnyl, Thrombo ASS);

- antihypoxants (Preductal MB, Preductal, Trimectal);

- anticoagulants (Warfarin).

Particularly preferred are those additional therapeutic agents that are used in the medical art to treat hypertension.

Preferably, for the purpose of treating hypertension, the combination pharmaceutical composition of the invention is administered from once daily to four times daily, each administration including one or two combination unit dosage forms. Each of the specific administration regimens within the described range is separately and specifically contemplated. Separate administration of two independently prepared unit dosage forms, each containing one of the activated potentiated forms of antibodies of the combination pharmaceutical composition is also contemplated.

The invention is further illustrated with reference to the appended non-limiting examples.

EXAMPLES

Example 1. Study of the efficacy of the combined drug based on ultra-low doses (ULD), i.e. the activated-potentiated solutions as described above, of antibodies to a C-terminal fragment of angiotensin II AT1 receptor and antibodies to endothelial NO synthase (mixture of homeopathic dilutions C12, C30 and C200) in

chronic heart failure (CHF) was conducted in 75 female Wistar rats (4-5 months old, weighing 220-250 g).

For chronic heart failure modeling all rats were receiving isadrine (isoproterenol hydrochloride, Sigma, Germany) 80 mg/kg twice with 24-hour interval. Animals (15 per group) were receiving the following drugs by gastric gavage: group 1 – 7.5 mL/kg of ULD of antibodies against a C-terminal fragment of angiotensin II AT1 receptor (mixture of homeopathic dilutions C12, C30 and C200), group 2 – 7.5 mL/kg of ULD of anti-endothelial NO synthase antibodies (mixture of homeopathic dilutions C12, C30 and C200), group 3 – 15 mL/kg of combined drug (mixture of homeopathic dilutions C12, C30 and C200), group 4 – 7.5 mL/kg (dose of 10 mg/kg) of losartan as a comparator, group 5 (control) – 7.5 mL/kg of distilled water.

The drug efficacy was assessed on Days 7, 14, 28 after repeated isadrine administration based on electrocardiogram and rheogram data, as well as the results of exercise tolerance test (swimming with weight load of 15% of the body weight at a water temperature of 24°C).

In 7 days following the second isadrine injection animals from all experimental groups developed myocardial damage manifesting in statistically significantly decreased myocardial contractility (decrease in systolic volume and cardiac output), cardiac electrical activity impairment (T-wave amplitude increase), proven lowering of exercise tolerance (swimming duration).

Following 14 days of the study drugs administration positive changes in evaluated parameters were noted. In 28 days significant improvement of the evaluated parameters was demonstrated compared to the results obtained on Day 7 (after the second isadrine injection) ($p<0.05$) (see Table 1).

Table 1. Changes in efficacy endpoints of CHF treatment (in % on Day 28 vs. Day 7)

Evaluated parameter	ULD of antibodies against C-terminal *fragment of* human angiotensin II AT1 receptor	ULD of anti-endothelial NO synthase antibodies	Combined drug based on ULD of antibodies to C-terminal fragment *of angiotensin II* AT1 receptor and antibodies to endothelial NO synthase	Losartan	Distilled water
T-wave amplitude	-22.37%	-15.81%	-30.03%	-31.64%	-7.7%
Heart rate	-10.75%	-8.57%	-22.43%	-21.28%	-6.74%
Systolic volume (by *Kubrick*)	46.98%	22.62%	69.74%	64.01%	15.0%
Cardiac output	35.11%	12.43%	49.40%	55.31%	7.13%

Thus, concomitant administration of the study preparations of ULD antibodies (combined drug) proved to be more effective compared to monotherapies, increased exercise tolerance, helped normalize cardiac electrical activity and cardiac cycle, systemic and intracardiac hemodynamics in rats with CHF. ULD antibodies combination demonstrated non-inferiority in terms of efficacy compared to losartan.

Example 2. Double blind, placebo-controlled clinical study of a combination of activated potentiated forms of antibodies to the C-terminal fragment of the angiotensin II AT1 receptor, in a mixture of homeopathic dilutions of C12, C30, C200, with activated potentiated form of antibodies to endothelial NO-synthase, in a mixture of homeopathic dilutions of C12, C30, C200, in human patients with chronic heart failure to evaluate key parameters of the CHF pathology.

80 patients (CHF of II-IV functional class (FC), left ventricular ejection fraction (LVEF) less than 40%) were divided in 4 equal treatment and control groups for a 6 months study. The background therapy was not discontinued (β-blocker bisoprolol, ACE inhibitor enalapril, aspirin (unless contraindicated); administration of diuretics, nitrates, digoxin was also admitted). Group 1 received the activated potentiated form of antibodies to a C-terminal fragment of the angiotensin II AT1 receptor (mixture of homeopathic dilutions C12, C30, C200) (3 tablets/day, n=20). Group 2 received the activated potentiated form of antibodies to endothelial NO-synthase (mixture of homeopathic dilutions C12, C30, C200) (3 tablets/day, n=20). Group 3 received the combination pharmaceutical composition comprising both activated potentiated form of antibodies to a C-terminal fragment of angiotensin II AT1-receptor (mixture of homeopathic dilutions C12, C30, C200) and activated potentiated form of antibodies to endothelial NO-synthase (mixture of homeopathic dilutions C12, C30, C200) (3 tablets/day, n=20). Group 4 received placebo (3 tablets/day, n=20) The groups were comparable in the initial study parameters: in age and sex, and severity (class of CHF and LVEF) and duration of the disease.

Before and after treatment, the patients were evaluated for the effect of the administered medications on vascular remodeling and endothelium dysfunction that is important for the CHF process and progression. The effects of the medications on the processes of vascular remodeling were evaluated by pulse wave velocity (PWV) ("Colson" system) in the carotid-femoral (CF) (elastic type) and carotid-radial (CR) (muscle type) segments of arteries.

Table 2 shows the dynamics in the rates of pulse wave velocity in the carotid-femoral (CF) (elastic type) and carotid-radial (CR) (muscle type) segments of arteries.

Table 2

Groups /Parameters	ULDs[1] of Abs[2] to C-terminal fragment of AT1 receptor of angiotensin II	ULD of Abs to endothelial NO-synthase	Combination of ULDs of Abs to C-end fragment of AT1 receptor of angiotensine II and ULD of Abs to endothelial NO-synthase	Placebo

	^	&	Δ%	^	&	Δ%	^	&	Δ%	^	&	Δ%
CF, m/c	9,7± 0.5	8± 0.6	-14.8*	10.1± 0.5	9.8± 0.4	-2.97	10.8± 0.3	8.6± 0.6	-20.3*	8.2± 0.4	8.2± 0.5	0.1
CR, m/c	8.6± 0.2	8.9± 0.3	2.9	8.8± 0.1	8.3± 0.3	-5.7	8.9± 0.5	7.6± 0.7	-15.6 *#$	9.1± 0.3	9.7± 0.3	6.4 *

(^) denotes initial value

(&) denotes 6 month after beginning of administration

(*) denotes difference from initial value is verifiable with p value < 0.05.

(#) denotes difference from the group receiving ULDs of Abs to C-terminal fragment AT1 receptor angiotensin II with verifiable difference in p value of < 0.05.

($) denotes difference from the group receiving ULDs of Abs to endothelial NO-synthase with significant difference in p value of < 0.05.

(1) ULD denotes ultra-low doses.

(2) Abs denotes antibodies.

After 6 months of treatment, only group 3 showed a proven effect of the claimed pharmaceutical composition on the stiffness of muscular type arteries. Group 1 which received ULD of antibodies to a C-terminal fragment of angiotensin II AT1 receptor, and group 3 which received the combination pharmaceutical composition of the invention showed a proven increase in the stiffness of elastic type arteries.

Example 3.

Double blind, placebo-controlled clinical study of a combination of activated potentiated forms of antibodies to the C-terminal fragment of angiotensin II AT1 receptor, in a mixture of homeopathic dilutions of C12, C30, C200, with activated potentiated form of antibodies to endothelial NO-synthase, in a mixture of homeopathic dilutions of C12, C30, C200, in human patients with chronic heart failure to evaluate key measurement of quality of life.

80 patients (CHF of II-IV functional class (FC), left ventricular ejection fraction (LVEF) less than 40%) were divided in 4 equal treatment and control groups for a 6 months study. The background therapy was not discontinued (bisoprolol β-blocker,

ACE inhibitor enalapril, aspirin (unless contraindicated); administration of diuretics, nitrates, digoxin was also admitted). Group 1 received the activated potentiated form of antibodies to a C-terminal fragment of angiotensin II AT1 receptor (mixture of homeopathic dilutions C12, C30, C200) (3 tablets/day, n=20). Group 2 received the activated potentiated form of antibodies to endothelial NO-synthase (mixture of homeopathic dilutions C12, C30, C200) (3 tablets/day, n=20). Group 3 received the combination pharmaceutical composition comprising both activated potentiated form of antibodies to a C-terminal fragment of angiotensin II AT1 receptor (mixture of homeopathic dilutions C12, C30, C200) and activated potentiated form of antibodies to endothelial NO-synthase (mixture of homeopathic dilutions C12, C30, C200) (3 tablets/day, n=20). Group 4 received placebo (3 tablets/day, n=20). The groups were comparable in the initial study parameters: in age and sex, and severity (class of CHF and LVEF) and duration of the disease. Before and after treatment, the patients were evaluated for the life quality (Minnesota and Kansas questionnaires), morphological parameters of the heart, and tolerance to physical exercise.

Table 3 shows the results of the study in the form of dynamics in the basic parameters of the treatment efficacy.

After 6 months of treatment, the patients in group 1 treated with ULD of antibodies to a C-terminal fragment of angiotensin II AT1 receptor showed a significant improvement of the life quality, improvement of the left ventricular systolic function, and an increased tolerance to physical exercise. Group 2 showed a proven decrease in the anxiety and depression levels and in the life quality, which were evaluated using the Kansas questionnaire. The study confirmed that the maximum therapeutic effect was achieved with the combination pharmaceutical composition of the invention in combination with the standard CHF therapy, which was administered to patients from group 3 that showed a proven positive dynamics in all parameters under study.

The combination of activated (potentiated) forms of antibodies to a C-terminal fragment of angiotensin II AT1 receptor and to endothelial nitric oxide synthase (NO-synthase) in the pharmaceutical composition of the invention (combination drug)

provides an unexpected synergistic therapeutic effect implying an enhanced influence on vascular remodeling and endothelium dysfunction that is critical for the CHF process and progression, as also on the improvement of the patients' life quality, on morphological parameters of the heart and tolerance to physical exercise, which is confirmed by clinical trials. The results are set forth in Table 3.

Table 3

Groups/ Parameters	ULD[1] of Abs[2] to C-terminal fragment of AT1 receptor of angiotensin II			ULD of Abs to endothelial NO-synthase			Combination of ULD of Abs to C-terminal fragment of AT1 receptor of angiotensin II and ULD of Abs to endothelial NO-synthase			Placebo		
	^	&	Δ%	^	&	Δ%	^	&	Δ%	^	&	Δ%
Minnesota[3]	47.5 ± 2.8	39.1± 3.8 **	-17.6	48.1± 3.7	40.8± 3.8	-15.2	43.9 ± 2.8	32.0 ± 4.9 ***$	- 27.1	48.3 ± 3.7	42.4 ±2.9 **	- 12.2
Kansas[4]	82.1± 2.3	70.1± 5.5 ***	-14.6	81.5± 2.5	72.0± 8.2 *	-11.7	87,7 ± 2.3	65.7 ±7.3 . ***$	- 25.1	83.8 ± 3.5	60.3 ±6.8	- 7.2

HADS[5]	15.3± 1.0	12.5± 0.9**	-18.5	16.2± 1.7	11.34 ±2.1 ***	-30.3	16.2 ± 1.3	8.4 ±0.9 *** # $$	- 48.1	17.3 ± 1.1	15.9 ±1.1	- 8.1
FC CHF[6]	2.7 ± 0.1	2.2± 0.1***	-17.3	2.9± 0.1	2.7±0 .2	- 7.3	3.0 ± 0.2	1.9 ±0.1 *** # $	- 36.6	2.7 ± 0.1	2.5 ±0.1	- 6.2
FF LV[7]	27.1± 0.9	33.6± 1.5**	24.0	28.2 ±1.5	25.3± 1.7	10.3	25.3 ± 1.1	34.6 ±1.9 *** # $	36.7	26.4 ± 1.1	28.0 ±1.4	6.3
6-minute walk test	378.7 ±12.4	419.6 ±13.7** **	10.8	383.1 ± 15.3	416.8 ±17.2	8.8	378.7 ±12.4	450.1 ±17.7 ** # $	18.9	390.5 ± 11.9	409.1 ±11.5	4.8

*, **, *** - p values < 0.05, 0.01 and 0.001, respectively

#- difference from group receiving ULDs of Abs to C-terminal fragment AT1 of angiotensin receptor II with verifiable with p value < 0.05

$, $$ - difference from the group receiving ULDs of Abs to endothelial NO-synthase is significant at p values of 0.05 and 0.01, respectively.

(1)-ULD means ultra low doses

(2) Abs means antibodies

(3) "Minnesota" denotes Minnesota Questionnaire

(4) "Kansas" denotes Kansas Questionnaire

(5) HADS denotes HADS total score

(6) FC CHF denotes patients with chronic heart failure, functional class

(7) FF LV denotes fraction of functioning of left vertical.

Example 4. Double blind placebo-controlled randomized clinical study of combination of the activated potentiated forms of antibodies to a C-terminal fragment of angiotensin II AT1 receptor, in a mixture of homeopathic dilutions of C12, C30, C200, with activated potentiated form of antibodies to endothelial NO-synthase, in a mixture of homeopathic dilutions of C12, C30, C200, in human patients with vegeto-vascular dystonia .

The clinical efficiency and safety of the combination pharmaceutical composition comprising activated-potentiated forms of antibodies to a C-terminal fragment of angiotensin II AT1 receptor and to endothelial NO-synthase (the mixtures of homeopathic dilutions C12, C30, C200) were tested on 60 male and female patients (male — 26.7% (n=16), female — 73.3% (n=44) of the total quantity of patients) with asthenia (more than 12 points according to "general asthenia" claim of the subjective asthenia scale MFI-20 (Multidimensional Fatigue Inventory)) and neurocirculatory asthenia (more than 15 points on the vegetative changes scale) aged 29-64 (average age 47.1 ± 1.77 years old).

The patients were randomized in two groups (n=30 each). The first group of patients received the combination pharmaceutical composition three times a day (1 pill each time). The second group patients took the placebo tablets three times a day (1 pill each time). The overall time of administration and patients monitoring lasted for 6 months.

The efficiency of treatment was evaluated by dynamics in the parameters of the subjective asthenia scale, questionnaires for estimating the anxiety and depression levels (Spielberger and Beck scale), questionnaire for evaluating the sleep and vegetative changes.

The dynamics in the vegetative and psychological state changes, in the patients' life quality during the treatment is shown in the Table 4.

Parameter	Combined Medication, n=30				Placebo, n=30			
	Visit 1	Visit 2 (4 weeks)	Visit 3 (12 weeks)	Visit 4 (24 weeks)	Visit 1	Visit 2 (4 weeks)	Visit 3 (12 weeks)	Visit 4 (24 weeks)
General asthenia (MFI-20 scale) (M±m)	12.9 ± 0.21	12.3 ± 0.29	11.5 ± 0.35 *** #	10.9 ± 0.27 *** ##	13.1 ± 0.26	12.9 ± 0.23	12.5 ± 0.17 ***	11.9 ± 0.19 ***
Physical asthenia (MFI-20 scale) (M±m)	12.3 ± 0.56	11.7 ± 0.49 **	11.2 ± 0.45 **	10.2 ± 0.39 *** #	12.3 ± 0.38	12.1 ± 0.29	11.7 ± 0.29 **	11.4 ± 0.21 **
Hypoactivity (MFI-20 scale) (M±m)	10.3 ± 0.50	10.1 ± 0.47	9.5 ± 0.42 *	9.1 ± 0.28 *	10.6 ± 0.63	10.1 ± 0.53 *	9.7 ± 0.50 **	9.5 ± 0.38 **
Motivation decrease (MFI-20 scale) (M±m)	9.60 ± 0.55	9.5 ± 0.47	8.6 ± 0.32 *	8.3 ± 0.27 *	9.9 ± 0.75	9.7 ± 0.57	9.4 ± 0.51	9.3 ± 0.48
Psychic asthenia (MFI-20 scale) (M±m)	10.2 ± 0.47	9.7 ± 0.44 *	9.5 ± 0.42 *	8.9 ± 0.41 ** #	10.8 ± 0.51	10.6 ± 0.43	10.5 ± 0.40	10.3 ± 0.38
Questionnaire of vegetative changes (total rate) (M±m)	28.9 ± 1.66	25.3 ± 1.26 **	22.1 ± 1.26 ***	17.6 ± 0.76 *** #	32.1 ± 3.36	29.5 ± 2.57 *	25.9 ± 2.42 ***	22.4 ± 2.08 ***
Questionnaire of sleep evaluation (total rate)	16.9 ± 0.44	18.4 ± 0.42 **	18.9 ± 0.34 ***	19.4 ± 0.29 *** #	16.6 ± 0.67	17.5 ± 0.56 **	18.1 ± 0.47 ***	18.2 ± 0.47 ***
Individual anxiety (Spielberger scale) (M±m)	37.6 ± 2.03	35.6 ± 1.42 *	35.1 ± 1.64 **	32.9 ± 1.23 ***	39.1 ± 3.05	38.7 ± 2.78	36.9 ± 2.45 *	36.9 ± 2.46 *
Reactive anxiety (Spielberger scale) (M±m)	39.3 ± 1.02	35.7 ± 0.72 *** #	34.5 ± 1.02 ***	32.4 ± 0.76 *** #	42.7 ± 2.65	40.3 ± 1.99**	38.3 ± 1.87 **	37.6 ± 1.81**
Beck questionnaire of depression (total rate) (M±m)	9.2 ± 0.44	8.4 ± 0.25 *	8.3 ± 0.27 *	7.8 ± 0.31 ** #	11.1 ± 1.43	10.5 ± 1.19 *	10.0 ± 0.93	9.9 ± 0.90 *

differences are significant vs the initial values at: * $p<0.05$, ** $p<0.01$, *** $p<0.001$.

differences are significant vs placebo group: # $p<0.05$, ## $p<0.01$, ### $p<0.001$.

It is shown that the administration of the combination pharmaceutical composition during 6 months resulted in a statistically significant decrease in the asthenia level on all MFI-20 subscales. The most significant improvements were observed in the following areas: general asthenia (from 12.9±0.21 to 10.9±0.27 points, $p<0.01$ of the placebo group), physical asthenia (from 12.3±0.56 to 10.2±0.39 points, $p<0.05$ of the placebo group), psychic asthenia (from 10.2±0.47 to 8.9±0.41 points, $p<0.05$ of the placebo group). After one month of treatment, basic group 1 showed a statistically proven decrease in the intensity of vegetative changes (according to the special-purpose questionnaire data), and after six months of treatment there was a statistically significant ($p<0.05$) difference of the achieved results (decrease of the total rate from 28.9±1.66 to 17.6±0.76) in comparison with the placebo group (decrease of the total rate from 32.1±3.36 to 22.4±2.08).

In addition, the administration of the combination pharmaceutical composition contributed to improving the psychological state of the patients in the study. A statistically significant decrease in the anxiety and depression levels was observed after one month of administration, and when the treatment was continued the positive effect was enhanced. After six months, group 1 showed a statistically significant ($p<0.05$) improvement in the reactive anxiety level on the Spielberger scale (decrease from 39.3±1.02 to 32.4±0.76) and the depression level according to the Beck questionnaire (decrease from 9.2±0.44 to 7.8±0.31) in comparison with the respective parameters of the placebo group (decrease from 42.7±2.65 to 37.6±1.81 and from 11.1±1.43 to 9.9±0.90 respectively). The results were confirmed by the positive dynamics ($p<0.001$ of the initial rates) in the parameters of the sleep evaluation questionnaire, and after six months of treatment, group 1 showed a statistically significant ($p<0.05$) difference in the total rate (increase from 16.9±0.44

to 19.4±0.29) in comparison with the placebo group (increase from 16.6±0.67 to 18.2±0.47).

Over the entire period of monitoring, the patients showed a high tolerability and no adverse effects.

The study showed that the combination pharmaceutical composition used in the study possesses antiasthenic effect, normalizes the vegetative state of patients with neurocirculatory dystonia and asthenia, and has anti-anxiety and anti-depression influence in the relevant patient population.

Example 5. Study of the combination of activated-potentiated forms of antibodies to the C-terminal fragment of the angiotensin II AT1 receptor, in a mixture of homeopathic dilutions of C12, C30, C200, with the activated-potentiated form of antibodies to endothelial NO synthase, in a mixture of homeopathic dilutions of C12, C30, C200, in SHR rats in a model of hypertension.

The combination of water solution of the activated-potentiated form of antibodies to a C-terminal fragment of the angiotensin II AT1 receptor, in a mixture of homeopathic dilutions of C12, C30, C200, and the activated-potentiated form of antibodies to endothelial NO synthase in a mixture of homeopathic dilutions of C12, C30, C200, was studied in the SHR rat hypertension model. Investigations were conducted on 40 SHR line male rats from (weight 350±50 g, age 4.5 - 5 months) with hypertension, which were divided into 4 groups of 10 animals each.

For 28 days, the animals were treated as follows. Group 1 – 2.5 ml/kg of the activated-potentiated form of antibodies to the C-terminal fragment of human angiotensin II AT1 receptor (a mixture of aqueous dilutions C12, C30, C200) in combination with 2.5 ml/kg of distilled water, Group 2 – 2.5 ml/kg of the activated-potentiated form of antibodies to endothelial NO synthase (a mixture of aqueous dilutions C12, C30, C200) in combination with 2.5 ml/kg of distilled water, Group 3 – 5 ml/kg of the combination pharmaceutical composition (a mixture of aqueous dilutions C12, C30, C200 for each component), and Group 4 – 5 ml/kg of distilled water.

Systolic blood pressure (SBP) of awake rats was measured with the aid of an indirect method in a tail artery (using a cuff) once a week and 9 hours after the last administration of medicines.

All tested compositions demonstrated hypotensive effect ($p<0.05$): by 28th day, systolic blood pressure (SBD) decreased in comparison with the initial level in Group 1 by – 20.6%; in Group 2 by 14.4%; in Group 3 by 27.6%. In the control Group 4, SBD changes were 1.6% in comparison with the initial values. The results demonstrate a clear synergistic hypotensive effect of the combination pharmaceutical composition.

Example 6. Study of the combination of the activated-potentiated forms of antibodies to a C-terminal fragment of angiotensin II AT1 receptor, in a mixture of homeopathic dilutions of C12, C30, C200, with the activated-potentiated form of antibodies to endothelial NO synthase, in a mixture of homeopathic dilutions of C12, C30, C200, in NISAG rats in a model of hypertension.

The combination water solution of the activated potentiated form of antibodies to a C-terminal fragment of angiotensin II AT1 receptor, in a mixture of homeopathic dilutions of C12, C30, C200, and the activated potentiated form of antibodies to endothelial NO synthase in a mixture of homeopathic dilutions of C12, C30, C200, was studied in the NISAG rat hypertension model. Investigations were conducted on 50 NISAG line male rats (weight 300 g, age 4 months) with hereditary stipulated stress-sensitive arterial hypertension, which were divided into 5 groups by 10 animals each.

The animals were given per orally, once a day and for 28 days, the following medications: Group 1 – 2.5 ml/kg of the activated-potentiated form of antibodies to a C-terminal fragment of human angiotensin II AT1 receptor (a mixture of dilutions C12, C30, C200) in combination with 2.5 ml/kg of distilled water; Group 2 – 2.5 ml/kg of the activated-potentiated form of antibodies to endothelial NO synthase (a mixture of dilutions C12, C30, C200) in combination with 2.5 ml/kg of distilled water; Group 3 - 5 ml/kg of the combination pharmaceutical composition (a mixture of homeopathic

aqueous dilutions C12, C30, C200 of each component); Group 4 - 5 ml/kg (10 ml/kg dose) of the comparison drug (losartan); and Group 5 - 5 ml/kg of distilled water.

Two times a week, 2 to 6 hours after administration of ULD antibodies and losartan, systolic blood pressure (SBP) was measured by an indirect method in a tail artery (using a cuff). The Table 5 shows the dynamics of changes in systolic blood pressure in NISAG line rats, measured by indirect method.

Table 5.

	Initial SBP in mmHg	SBP after 28 days of medicine administration in mmHg	Δ in comparison with the initial level, in mmHg	% of the initial level
ULD antibodies to C-terminal fragment of angiotensin II AT1receptor	176	150	-26	- 14.7 %
ULD antibodies to endothelial NO synthase	175	164.5	-10.5	-6%
ULD antibodies to C-terminal fragment of angiotensin II AT1receptor and to endothelial NO synthase	179.5	140	-39.5	-22%
Losartan	173.5	140.5	-33	-19%
Control (distilled water)	181	178	-3	-1.6%

Example 7. Study of correction of endothelial dysfunction

Wistar rats weighed 250 - 300 g were divided into 4 groups. The 1st group received distilled water 9 ml/kg/day (every day, gastrointestinal introduction). The 2nd group received L-NAME (L-NG-nitroarginine methyl ester, which is known to inhibit endothelial isoform, and thus is believed to simulate endothelial dysfunction)

at 12.5 mg/kg. The third group received L-NAME (12.5 mg/kg) in combination with a mixture of C12, C30, and C200 homeopathic dilutions of polyclonal rabbit antibodies to human endothelial NO synthase at 9 ml/kg/day. The 4th group received L-NAME (12.5 mg/ml) in combination with a mixture of C12, C30, and C200 homeopathic dilutions of polyclonal rabbit antibodies to human endothelial NO synthase at 9 ml/kg/day and mixture of C12, C30, C200 homeopathic dilutions of polyclonal rabbit antibodies to a C-terminal fragment of AT1 receptor of angiotensin II at 9 ml/kg/day.

Endothelial dysfunction was simulated by introducing L-NAME at 12.5 mg/ml/day in the course of 28 days. On day 29 from the beginning of the experiment, under anesthesia (sodium thiopental at 50 mg/kg), a catheter was inserted into the left carotid artery to register parameter of arterial pressure (AP). Bolus introduction of the pharmacological agent was made into right femoral vein. The following parameters were measured: systolic arterial pressure (SAP), diastolic arterial pressure (DAP), and frequency of heart beat, which were measured in real time by sensor TSD104A measurement apparatus MP100 made by Biopac System, Inc., USA. The following functional probes were used: endothelium-dependent vasodilation (EDV), intra-vein introduction of acetylcholine (AC) in the dose of 40 μg/kg, endothelium-independent vasodilation (EIV) via intravein introduction of sodium *nitroprusside* at 30 μ/kg.

The degree of endothelial dysfunction was evaluated via the coefficient of endothelial dysfunction as the ratio of the area of the triangle under the trend of reaction of stabilization of arterial pressure (AP) as a response to introduction of nitroprusside to the area of the triangle under the trend of reaction of stabilization of arterial pressure as a response to introduction of acetylcholine.

The results of the experiments are presented in Table 6.

Table 6.

Groups	Functional Probe	SAP, mm, HG	DAP, mm HG	Vascular reaction observed with EDV with acetyl choline EIV with sodium *nitroprusside*	CED, (relative units)
Control (daily in-stomach introduction of distilled water at 9 ml/kg/day	*Initial*	159.2 ±5.4	124.2 ± 4.7		1.2±0.1
	Acetyl choline	96.9 ± 6,7	52.0 ±3.0	3071.2± 501.1	
	Sodium Nitroprussid e	113.8 ± 6,1	55 ± 2,4	3617.2± 560.1	
L-NAME	*Initial*	204.8±10*	164.2±5.9*		3.5±0.5*
	Acetyl choline	111.3±7.4	64.7±4.3*	3700.2± 536.9	
	Sodium Nitroprussid e	118.2±9,9	61.4±4.4	11922.8± 1838.9*	
L-NAME in combination with a mixture of C12, C30, and C200 homeopathic dilutions of polyclonal rabbit antibodies to human endothelial NO-synthase	*Initial*	230.1±8.8*	175.1±6.4*		1.8±0.2**
	Acetyl choline	116.4±4.0*	73.5±3.5*	5826.0± 801.2**	
	Sodium Nitroprussid e	108.1±4.6	60±3.6	9628.5± 970.1*	
L-NAME in combination with a mixture of C12, C30, and C200 homeopathic dilutions of polyclonal rabbit antibodies to human endothelial NO-synthase and mixture of C12, C30, C200 homeopathic dilutions of polyclonal rabbit antibodies to C-terminal fragment of AT1 receptor of angiotensin II	*Initial*	213.6±4.6*	166.8±2.7*		1.4±0.1**
	Acetyl choline	116.9±5.5*	73.3±3.4*	3295.3± 201.4	
	Sodium Nitroprussid e	122.3±4.6	70.5±4.5*	4546.2± 299.4**	

* - p<0,05 in comparison with the control group; ** - p<0,05 in comparison with the L-NAME group. S – area under the curve of restoration of arterial hypertension per pharmacological probes, , CED-coefficient of endothelial dysfunction.

What is claimed is:

1. A combination pharmaceutical composition for administration to a patient associated with at least one symptom of at least one condition selected from the group consisting of chronic heart failure, asthenia, vegetative vascular dystonia, anxiety associated with chronic heart failure, depression associated with chronic heart failure and hypertension, the combination pharmaceutical composition comprising a) an activated-potentiated form of an antibody to angiotensin II AT1 receptor, and b) an activated-potentiated form of an antibody to endothelial NO-synthase, the activated potentiated forms produced by homeopathic technology.

2. The combination pharmaceutical composition of claim 1, wherein said activated-potentiated form of an antibody to angiotensin II AT1 receptor is an activated-potentiated form of an antibody to the C-terminal fragment of the angiotensin II AT1 receptor.

3. The combination pharmaceutical composition of claim 1, wherein said pharmaceutical composition is administered to said patient suffering from a condition associated with a reduced quality of life and wherein said administration of said pharmaceutical composition to said patient improves said quality of life of said patient.

4. The combination pharmaceutical composition of claim 1, wherein said activated-potentiated form of an antibody to angiotensin II AT1 receptor is in the form of a C12, C30, or C200 homeopathic dilution or a mixture thereof.

5. The combination pharmaceutical composition of claim 1, wherein said activated-potentiated form of an antibody to angiotensin II AT1 receptor is in the form of a mixture of C12, C30, and C200 homeopathic dilutions impregnated onto a solid carrier.

6. The combination pharmaceutical composition of claim 1, wherein said activated-potentiated form of an antibody to endothelial NO-synthase is in the form of a C12, C30, or C200 homeopathic dilution or a mixture thereof.

7. The combination pharmaceutical composition of claim 1, wherein said activated-potentiated form of an antibody to endothelial NO-synthase is in the form of mixture of C12, C30, and C200 homeopathic dilutions impregnated onto a solid carrier.

8. The combination pharmaceutical composition of claim 1, which is prepared by impregnating a solid carrier with a mixture of i) said activated-potentiated form of an antibody to endothelial NO-synthase is in the form of mixture of C12, C30, and C200 homeopathic dilutions, and ii) said activated-potentiated form of an antibody to angiotensin II AT1 receptor is in the form of mixture of C12, C30, and C200 homeopathic dilutions.

9. The combination pharmaceutical composition of claim 1, wherein said activated-potentiated form of an antibody to angiotensin II AT1 receptor is a monoclonal, polyclonal or natural antibody.

10. The combination pharmaceutical composition of claim 9, wherein said activated-potentiated form of an antibody to angiotensin II AT1 receptor is a polyclonal antibody.

11. The combination pharmaceutical composition of claim 8, wherein said activated-potentiated form of an antibody to angiotensin II AT1 receptor is prepared by successive centesimal homeopathic dilutions coupled with shaking of every dilution.

12. The combination pharmaceutical composition of claim 1, wherein said activated-potentiated form of an antibody to endothelial NO-synthase is a monoclonal, polyclonal or natural antibody.

13. The combination pharmaceutical composition of claim 12, wherein said activated-potentiated form of an antibody to endothelial NO-synthase is a polyclonal antibody.

14. The combination pharmaceutical composition of claim 8, wherein said activated-potentiated form of an antibody to endothelial NO-synthase is prepared by successive centesimal homeopathic dilutions coupled with shaking of every dilution.

15. A combination pharmaceutical composition for administration to a patient suffering from at least one symptom of chronic heart failure, asthenia, vegetative dystonia, or hypertension, said composition comprising a) an activated-potentiated form of an antibody to angiotensin II AT1 receptor, and b) an activated-potentiated form of an antibody to endothelial NO-synthase, the activated potentiated forms produced by homeopathic technology.