[NAME OF DOCUMENT] SPECIFICATION

[TITLE OF THE INVENTION] Drug For Treatment of Tinnitus Patients

[Technical Field]

[0001]

The present invention relates to a drug for treatment of tinnitus patients.

[Background Art]

[0002]

Inner ear damage is a major problem in modern society. Tinnitus, in association with hearing impairment, is a common condition encountered with inner ear damage. Tinnitus is defined as either "reception of sound among auditory stimulation lacking from the external environment" or "an abnormal auditory phenomenon produced by sensation of a sound, despite the lack of a sound source outside of the body". Tinnitus can be produced by damage to any part of the auditive pathway from the external ear to the central auditive pathway, but it is generally produced by inner ear hearing loss, and the condition of tinnitus is characterized by increased abnormal nerve activity in the central auditive pathway due to reduced input of auditory information resulting from cochlear damage. For the individual patient, tinnitus is sometimes tolerable but in some cases can lead to anxiety, depression, insomnia, disability or mental distress.

[0003]

A number of factors are involved in tinnitus, but PTL 1, for example, teaches that neramexane and its pharmaceutically acceptable salts are effective for

treatment of patients suffering from tinnitus caused by stress or acute hearing loss (sudden hearing loss).

[Citation List]

[Patent Literature]

[0004]

[PTL 1] Japanese Patent Publication No. 2014-502981

[Summary of the Invention]

[Problems to be Solved by the Invention]

[0005]

Incidentally, PTL 1 does not mention or suggest the possibility that more effective treatment can be carried out if the patient group is a group with a potentially greater drug effect among patients suffering from tinnitus caused by stress or sudden hearing loss.

[0006]

It is therefore an object of the present invention to provide a drug for treatment of tinnitus patients that allows more effective treatment to be carried out specifically for a patient group expected to experience a greater drug effect.

[Means for Solving the Problems]

[0007]

Specifically, the invention provides the following [1] to [5].

[1] A drug for treatment of patients having tinnitus associated with sudden hearing loss, comprising neramexane or a pharmaceutically acceptable salt thereof, wherein the patients have morbidity period of 48 months or longer.

[2] A drug for treatment of patients having

tinnitus associated with sudden hearing loss, comprising neramexane or a pharmaceutically acceptable salt thereof, wherein the patients have suffering period of less than 6 months.

[3] A drug for treatment of patients having tinnitus associated with sudden hearing loss, comprising neramexane or a pharmaceutically acceptable salt thereof, wherein the patients have serious degree of anxiety.

[4] A drug for treatment of patients having tinnitus associated with sudden hearing loss, comprising neramexane or a pharmaceutically acceptable salt thereof, wherein the patients have serious degree of depression.

[5] A drug for treatment of patients having tinnitus associated with sudden hearing loss, comprising neramexane or a pharmaceutically acceptable salt thereof, wherein the patients have two or more characteristics selected from the group consisting of (i) morbidity period of 48 months or longer; (ii) suffering period of less than 6 months; (iii) serious degree of anxiety; and (iv) serious degree of depression.

[Effect of the Invention]

[0008]

According to the invention it is possible to provide a drug for treatment of tinnitus patients that allows more effective treatment to be carried out specifically for a patient group expected to experience a greater drug effect.

[Mode for Carrying Out the Invention]

[0009]

The terms and symbols used herein will now be explained with a more detailed description of the invention, with the understanding that the invention is not limited thereto.

[0010]

Neramexane (chemical name: 1-amino-1,3,3,5,5-pentamethylcyclohexane) is disclosed in US Patent No. 6,034,134 and No. 6,071,966, for example. This compound has been found to be useful for treatment of various diseases and particularly for certain neuropathies. The therapeutic effect of neramexane is putatively due to inhibition of the effect of excess glutamic acid at neuronic N-methyl-D-aspartic acid (NMDA) receptors. For this reason, the compound is classified as an NMDA receptor antagonist. In addition, it has been disclosed that neramexane exhibits inhibiting activity on α9/α10 nicotinic acetylcholine receptors (Plazas, et al., Eur J Pharmacol., 2007 Jul. 2; 566(1-3):11-19) and 5-HT_3 receptors.

[0011]

For the purpose of this embodiment, neramexane may be used in any form including as a pharmaceutically acceptable salt, solvate compound, isomer, conjugant, prodrug, polymorphism, derivative or a mixture of the foregoing. The term "neramexane" as used herein, unless otherwise specified, is to be interpreted as also referring to a pharmaceutically acceptable salt, solvate compound, conjugant, prodrug, polymorphism or derivative thereof, or a mixture of the foregoing.

[0012]

For the purpose of the present specification, the term "pharmaceutically acceptable salt" means a salt of 1-amino-1,3,3,5,5-pentamethylcyclohexane that can be obtained by combination with an inorganic or organic acid, and that does not affect human safety and/or that is sufficiently accepted by humans after administration. Examples of pharmaceutically acceptable salts include, but are not limited to, acid addition salts such as salts produced from hydrochloric acid, hydrobromic acid, hydroiodic acid, perchloric acid, sulfuric acid, nitric acid, phosphoric acid, acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, carbonic acid, cinnamic acid, mandelic acid, methanesulfonic acid (mesylic acid), ethanesulfonic acid, hydroxyethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, cyclohexanesulfamic acid, salicylic acid, p-aminosalicylic acid, 2-phenoxybenzoic acid and 2-acetoxybenzoic acid, with mesylic acid being preferred. Such salts (or similar salts) can all be prepared by conventional means. The nature of the salt is not essential so long as it is non-toxic and does not substantially interfere with the desired pharmacological activity. Conversion of 1-amino-1,3,3,5,5-pentamethylcyclohexane to a pharmaceutically acceptable salt thereof can be accomplished by mixing 1-amino-1,3,3,5,5-pentamethylcyclohexane with at least one molecular equivalent of the selected acid in the presence of an inert organic solvent using a

conventional method. Isolation of the salt can be accomplished by a method known in the art, such as by causing precipitation with a nonpolar solvent that exhibits limited solubility for the salt (for example, ether).

[0013]

The term "pharmaceutically acceptable" as it relates to a component (or substance, compound or agent) encompasses components (or substances, compounds or agents) that do not affect human safety and/or that are sufficiently accepted by humans after administration. Typically, when used herein, the term "pharmaceutically acceptable" means listed in the Pharmacopeia as being accepted by a regulatory agency or being generally approved, for use in mammals and more specifically humans.

[0014]

The terms "polymorphism" and "polymorphism-type" include neramexane or pharmaceutically acceptable salts thereof, that forms variety of crystal structures or lattices.

[0015]

The term "prodrug" encompasses substances derived from neramexane or substances serving as sources for preparation of neramexane, such substances being administered in forms having little or no activity in the body compared to neramexane itself.

[0016]

The term "solvate compound" encompasses substances formed by bonding of 1-amino-1,3,3,5,5-pentamethylcyclohexane with a solvent molecule or its

attraction of a solvent molecule. A solvate compound where the solvent is water is known as a "hydrate".

[0017]

The term "conjugant" encompasses substances formed by covalent bonding or non-covalent bonding of neramexane with a carrier.

[0018]

The term "derivative" refers to neramexane having the amino group derivatized with 1 or 2 alkyl groups.

[0019]

The term "isomer" refers to the possible stereoisomers of neramexane, such as conformational isomers and enantiomers or diastereomers.

[0020]

The terms "approximately" and "about" usually means within 20%, or within 10%, such as within 5%, of a given value or range.

[0021]

The terms "treat" and "treatment" are used herein in the sense of alleviation or reduction of at least one condition or symptom of a patient. Also as used herein, the term "treat" means halting or delaying onset (the period before condition is clinically manifested) and/or reducing disease progression or risk of exacerbation.

[0022]

A therapeutic effect can be evaluated by physician inquiry using a questionnaire form such as TRSw (Tinnitus Rating Scale One-Week Version) (Acta Otolaryngol., 2013, 133(5), 491-498).

[0023]

As used herein, the term "tinnitus" encompasses all symptoms including subjective and objective tinnitus.

[0024]

Tinnitus that is to be treated by the drug of the invention is that associated with sudden hearing loss. The tinnitus may be occurring before onset of sudden hearing loss, or occurring simultaneously with onset of sudden hearing loss, or having occurred subsequent to (after) onset of sudden hearing loss.

[0025]

As used herein, "sudden hearing loss" means a high degree of sound perception hearing impairment of unknown cause, with sudden onset. More specifically, it means such hearing loss occurring once or over a period of up to 3 days, in which the ability to detect sound is totally or partially lost. Hearing impairment is clinically diagnosed by increased auditory threshold level in a pure tone audiogram. The generally used criterion is, for example, increase in the auditory threshold value of 30 dB or greater for 3 continuous pure tone frequencies in a pure tone audiogram during onset.

[0026]

As used herein, the term "sudden hearing loss" is used in the same sense as the terms "acute hearing loss", "acute hearing impairment" and "spontaneous hearing loss".

[0027]

Also as used herein, the term "sound perception hearing impairment" refers to hearing impairment

considered to be accompanied by organic lesion in the internal ear or at a site from the internal ear to the auditory center.

[0028]

Incidentally, "sudden hearing loss" is clinically distinguished from noise-induced hearing impairment and hearing loss caused by noise trauma including acoustic trauma deafness.

[0029]

As used herein, the term "morbidity period" means the period from onset of tinnitus until the start of treatment, and the term "suffering period" means the period from being troubled by tinnitus until the start of treatment. The morbidity period and the suffering period can be determined by physician inquiry or questionnaire directed toward the patient.

According to a particular embodiment, the tinnitus patient is specified as having the feature of having a "morbidity period" at the time specified by the patient by response to questioning relating to the period of onset of tinnitus.

According to a particular embodiment, the tinnitus patient is specified as having the feature of having a "suffering period" at the time specified by the patient by response to questioning relating to the period of being troubled by tinnitus.

[0030]

As used herein, "serious degree of anxiety" means an anxiety score of greater than 10 on the HADS (Hospital Anxiety and Depression Scale), and according to a particular embodiment it means greater than 10 and

no greater than 14. Also as used herein, "serious degree of depression" means a depression score of greater than 10 on the HADS, and according to a particular embodiment it means greater than 10 and no greater than 14.

[0031]

The drug of the invention may contain only neramexane or its pharmaceutically acceptable salt alone, or it may contain neramexane or its pharmaceutically acceptable salt together with carriers or the like. The dosage form of the drug of the invention may be as a solid formulation, such as capsules, tablets or a similar form.

[0032]

The drug of the invention can also be orally administered as a semi-solid or liquid formulation.

[0033]

For a solid formulation in the form of tablets or capsules, the neramexane or its pharmaceutically acceptable salt may be combined with the following, for example: nontoxic pharmaceutically acceptable excipients such as binders (for example, gelatinized corn starch, polyvinylpyrrolidone or hydroxypropyl methyl cellulose); fillers (for example, lactose, sucrose, glucose, mannitol, sorbitol and other reducing or non-reducing sugars, microcrystalline cellulose, calcium sulfate or calcium hydrogenphosphate); lubricants (for example, magnesium stearate, talc or silica, stearic acid, sodium stearyl fumarate, glycerin behenate, calcium stearate and similar substances); disintegrators (for example, potato starch or starch

sodium glycolate); or moistening agents (for example, sodium lauryl sulfate), coloring agents and flavoring agents, gelatin, sweetener, natural and synthetic rubber (for example, acacia, tragacanth or alginic acid), buffer salts, carboxymethyl cellulose, polyethylene glycol, waxes, and similar substances.

[0034]

Tablets can be coated with a concentrated sugar solution which may contain, for example, gum arabic, gelatin, talc, titanium dioxide or similar substances. Alternatively, tablets may be coated with a polymer that dissolves in a readily volatile organic solvent or a mixture of organic solvents. According to a specific mode, neramexane is compounded into immediate release (IR) or modified release (MR) tablets. An immediate release solid dosage form allows release of most or all (for example, 90% or more) of the active ingredient in a short period of time such as 60 minutes or less, and allows rapid absorption of the drug.

[0035]

A modified release solid oral drug allows sustained release of the active ingredient over a prolonged period, in order to maintain a therapeutically effective blood plasma level for long periods, and/or to examine other pharmacokinetic properties of the active ingredient. For example, neramexane mesylate can be formulated as a modified release dosage form (for example, a modified release tablet) for supply of a 50 mg dosage of neramexane mesylate.

[0036]

For a soft gelatin capsule formulation, neramexane or its pharmaceutically acceptable salt may be compounded together with a vegetable oil or polyethylene glycol, for example. Hard gelatin capsules may contain granules of the active substance, using any of the aforementioned excipients for tablets, such as lactose, saccharose, sorbitol, mannitol, starch (for example, potato starch, corn starch or amylopectin), cellulose derivatives or gelatin. Also, a liquid or semi-solid drug may be filled into hard gelatin capsules.

[0037]

Neramexane or its pharmaceutically acceptable salt may also be introduced into microspheres or microcapsules produced from polyglycolic acid/lactate acid (PGLA) (for example, see US Patent No. 5,814,844, No. 5,100,669, No. 4,849,222; International Patent Publication No. WO95/11010 and No. 93/07861). A biocompatible polymer, for example, a polylactic acid, polyglycolic acid, polylactic acid and polyglycolic acid copolymer, poly(ε-caprolactone), polyhydroxybutyric acid, poly(ortho ester), polyacetal, polyhydropyran, polycyano acrylate, or a hydrogel crosslinked or amphiphilic block copolymer, may be used to achieve modified release of the drug.

[0038]

A semi-solid or liquid formulation of neramexane or its pharmaceutically acceptable salt may also be used. Neramexane may constitute 0.1 to 99 wt% of the formulation, and more specifically, 0.2 to 50 wt% for a suitable formulation that is to be administered orally.

[0039]

Neramexane or its pharmaceutically acceptable salt may be administered as a modified release formulation. A modified release dosage form provides a means of improving patient compliance and ensuring effective and safe treatment, by reducing incidence of side-effects. Compared to an immediate release dosage form, a modified release dosage form has extended pharmacological action following administration and lower plasma concentration of drug over the administered period, whereby it is possible to eliminate or reduce sharp peaks.

[0040]

A modified release dosage form may comprise a core which is coated with or containing the drug. The core is then coated with a sustained-release modified polymer in which the drug is dispersed. The sustained-release modified polymer gradually disintegrates and releases the drug over time. It is thus prepared so that the outermost layer of the composition is effectively reduced, so that when the composition is exposed to an aqueous environment, i.e. in the gastrointestinal tract, the drug diffuses through the coating layer. The net diffusion rate of the drug will depend on the ability of gastric juice to penetrate the coating layer or matrix, and on the solubility of the drug itself.

[0041]

According to another mode of the invention, neramexane or its pharmaceutically acceptable salt is prepared as an oral liquid formulation. A liquid

formulation for oral administration may be in the form of, for example, a liquid, syrup, emulsion or suspension, or it may be provided as a dry product to be reformulated with water or another appropriate vehicle before use. A formulation for oral administration may be appropriately formulated to provide controlled or extended release of the active compound.

[0042]

For oral administration of a liquid form, neramexane or its pharmaceutically acceptable salt may be combined with a nontoxic pharmaceutically acceptable inert carrier (for example, ethanol, glycerol or water), a suspending agent (for example, sorbitol syrup, a cellulose derivative or a hydrogenated edible fat), an emulsifier (for example, lecithin or acacia), a nonaqueous vehicle (for example, almond oil, an oil-based ester, ethyl alcohol or a fractionated vegetable oil), a preservative (for example, methyl or propyl-p-hydroxybenzoate or sorbic acid), and similar substances. A stabilizer such as an antioxidant (BHA, BHT, propyl gallate, sodium ascorbate or citric acid) may also be added to stabilize the dosage form. For example, a solution may contain a mixture of approximately 0.2 to approximately 20 wt% neramexane, a sugar, and ethanol, water, glycerol and propylene glycol. Optionally, such a liquid formulation may contain a coloring agent, flavoring agent, saccharin and carboxymethyl-cellulose as a thickener or other excipient.

[0043]

According to another mode, a therapeutically

effective dose of neramexane or its pharmaceutically acceptable salt is administered as an oral solution containing a preservative, sweetener, solubilizing agent and solvent. An oral solution may contain one or more buffers, flavoring agents or additional excipients. According to yet another mode, peppermint or other flavoring agents are added to a neramexane oral liquid formulation.

[0044]

For inhaled administration, neramexane can be conveniently supplied in the form of an aerosol atomized presentation from a compressed pack or nebulizer, using an appropriate propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoromethane, carbon dioxide or another suitable gas. In the case of a compressed aerosol, the administration unit can be established by providing bubbles for supply of a metered dose. Gelatin capsules and a cartridge for use in an inhalator or syringe may be included so as to contain a powder mixture of a compound and suitable powder base, such as lactose or a starch.

[0045]

A solution for parenteral administration by injection may be formulated as an aqueous solution of a pharmaceutically acceptable salt of neramexane at a concentration of approximately 0.5% to approximately 10 wt%. Such a solution may also contain a stabilizer and/or buffering agent, and may be provided as an ampule for different administration units.

[0046]

The drug of the invention may be directly injected by, for example, bolus injection or continuous injection, in a parenteral manner, i.e. intravenous (i.v.), intracerebroventricular (i.c.v.), subcutaneous(s.c.), intraperitoneal (i.p.), intramuscular (i.m.), intratympanic (i.t.), subdermal (s.d.) or intradermal (i.d.) administration. A formulation for injection may be provided in a unit dosage form, such as an ampule or multidose container, together with an added preservative. On the other hand, a pharmaceutically acceptable salt of neramexane may exist as a powder form for reformulation with a suitable vehicle, for example, aseptic pyrogen-free water before use.

[0047]

The drug of the invention may be provided as a medical pack or kit comprising one or more containers comprising neramexane or its pharmaceutically acceptable salt and optionally the many components in the formulation. According to a specific mode, neramexane is provided as an oral solution (2 mg/ml) for administration using a 2-teaspoon syringe (dosage KORC^{R}). An individual oral syringe has lines on the right side (lowered tip) of the syringe showing teaspoon units and blue hatch marks for measurement with the lines, on the left side of the syringe showing ml units.

[0048]

The optimal therapeutically effective dose can be determined in consideration of the form of administration of the drug, the patient (for example,

body weight, health, age and gender), and the preference and experience of the acting physician.

[0049]

The dosing unit for rectal administration may be prepared in the form of a solution or suspension, or a suppository or retention enema containing neramexane mixed with a triglyceride base, or a gelatin rectal capsule containing neramexane mixed with a vegetable oil or paraffin oil.

[0050]

The toxicity and therapeutic effect of neramexane or its pharmaceutically acceptable salt may be measured, for example, by determining the LD_{50} (50% lethal dose for a group) and ED_{50} (50% therapeutically effective dose for a group), in a standard treatment method for experimental animals. The dose ratio between the therapeutic effect and toxicity effect is the therapeutic index, and it can be expressed as the ratio LD_{50}/ED_{50}. Neramexane or its pharmaceutically acceptable salt/composition preferably has a high therapeutic index.

[0051]

An appropriate daily dose for neramexane or its pharmaceutically acceptable salt for human treatment is approximately 0.01 to 10 mg/kg body weight for oral administration and 0.001 to 10 mg/kg body weight for parenteral administration. For example, a suitable daily dosage of neramexane mesylate for adults may be a dose of 25 mg, 50 mg or 75 mg. An equimolar amount of a separate pharmaceutically acceptable salt, solvate compound, isomer, conjugant, prodrug, polymorphism or

derivative, such as neramexane hydrochloride, is also suitable.

[0052]

Generally, neramexane or its pharmaceutically acceptable salt, such as neramexane mesylate is administered in a range of about 5 mg to about 150 mg/day, about 5 mg to about 100 mg/day or about 5 mg to about 75 mg/day, or at about 50 mg/day or about 75 mg/day.

[0053]

The daily doses indicated throughout the present specification may be administered, for example, once, twice or three times a day, as single or double dose units.

[0054]

The treatment period may be a short period such as several weeks (for example, 8 to 16 weeks), or it may be a long period until the attending physician judges that no further treatment is necessary.

[0055]

The drug of the invention may be administered in a form with a dose-setting scheme (titration scheme). The term "dose-setting scheme" means a treatment method such as carried out in the examples of the present specification. The patient is initially administered a low dose of neramexane or its pharmaceutically acceptable salt, and is then given the same dose or a higher dose during the treatment period.

[Examples]

[0056]

The invention will now be further explained by

examples, with the understanding that the scope of the invention is not limited by the examples.

[0057]

Film coated tablets comprising 12.5 mg neramexane mesylate were produced by the method disclosed in International Patent Publication No. WO2009/033649.

[0058]

The efficacy of neramexane mesylate on patients with tinnitus associated with sudden hearing loss was evaluated in a 24-week, placebo controlled, randomized, double-blind comparative trial.

[0059]

The film coated tablets comprising 12.5 mg neramexane mesylate or placebo tablets were administered for 24 weeks to patients having tinnitus. The dosage was started from 12.5 mg/day, and gradually increasing the dose to 50 mg/day over 4 weeks, and maintaining the same dose thereafter.

[0060]

The therapeutic effect of neramexane mesylate for the patients was evaluated using the TRSw score. Also, the state of anxiety or depression of the patients was evaluated using the HADS score. The evaluation results are shown in Table 1. Statistical analysis was performed using a mixed-effect model repeated measure (MMRM) taking into consideration the covariance structure of error for the patient, with the change in TRSw score from before administration of neramexane mesylate tablets or placebo tablets (0 weeks) to each evaluation time point as the response variable, and with the drug-administered group, evaluation time point,

interaction between drug-administered group and evaluation time point, 0-week TRSw score, gender and body weight as anchor effects. The numerical values in the table represent least mean squares for the change in TRSw score at 16 weeks after administration and 24 weeks after administration. A change in score of less than 0 indicates a higher therapeutic effect.

[0061]

[Table 1]

Table 1 Therapeutic effect of neramexane mesylate

Test group	Change in TRSw score		
	Neramexane	Placebo	Neramexane - placebo
Tinnitus associated with sudden hearing loss	-2.3	-0.6	-1.8
Tinnitus associated with sudden hearing loss, together with morbidity period of 48 months or longer	-4.0	0.2	-4.2
Tinnitus associated with sudden hearing loss, together with suffering period of less than 6 months	-3.7	0.0	-3.8
Tinnitus associated with sudden hearing loss, together with HADS (anxiety) of >10	-2.4	1.3	-3.7
Tinnitus associated with sudden hearing loss, together with HADS (depression) of >10	-3.1	0.6	-3.7

[0062]

Neramexane mesylate exhibited a clear therapeutic

effect compared to placebo for patients affected by tinnitus associated with sudden hearing loss. Furthermore, surprisingly, neramexane mesylate exhibited an unexpectedly excellent therapeutic effect for patients suffering from tinnitus associated with sudden hearing loss, in a group with a morbidity period of 48 months or longer, in a group with a suffering period of shorter than 6 months, in a group with an anxiety value of greater than 10 according to HADS, and in a group with a depression value of greater than 10 according to HADS. Thus, neramexane mesylate was found to be a highly effective treatment agent for tinnitus, for these specific groups among tinnitus associated with sudden hearing loss.

[NAME OF DOCUMENT] CLAIMS

[CLAIM 1]

A drug for treatment of patients having tinnitus associated with sudden hearing loss, comprising neramexane or a pharmaceutically acceptable salt thereof, wherein the patients have morbidity period of 48 months or longer.

[CLAIM 2]

A drug for treatment of patients having tinnitus associated with sudden hearing loss, comprising neramexane or a pharmaceutically acceptable salt thereof, wherein the patients have suffering period of less than 6 months.

[CLAIM 3]

A drug for treatment of patients having tinnitus associated with sudden hearing loss, comprising neramexane or a pharmaceutically acceptable salt thereof, wherein the patients have serious degree of anxiety.

[CLAIM 4]

A drug for treatment of patients having tinnitus associated with sudden hearing loss, comprising neramexane or a pharmaceutically acceptable salt thereof, wherein the patients have serious degree of depression.

[CLAIM 5]

A drug for treatment of patients having tinnitus associated with sudden hearing loss, comprising neramexane or a pharmaceutically acceptable salt thereof, wherein the patients have two or more characteristics selected from the group consisting of

(i) morbidity period of 48 months or longer; (ii) suffering period of less than 6 months; (iii) serious degree of anxiety; and (iv) serious degree of depression.