

DESCRIPTION

Title of Invention: DRUG FOR PREVENTING AND/OR TREATING
POLYCYSTIC KIDNEY DISEASE

5 Technical Field

The present invention relates to a drug for preventing and/or treating polycystic kidney disease (PKD).

Background Art

Polycystic kidney disease is classified into ADPKD
10 (autosomal dominant polycystic kidney disease) and ARPKD
(autosomal recessive polycystic kidney disease). In both types of
polycystic kidney disease, many cysts develop in the cortex and
medulla of the kidney, leading to kidney dysfunction accompanied
by substantial atrophy and fibrosis. As the disease progresses,
15 the kidneys develop hypertrophy, leading to kidney failure
requiring dialysis.

In cyst epithelial cells wherein cysts develop from
tubular cells, cyclic AMP (cAMP) activates protein kinase A (PKA),
and a series of MAP kinase (MAPK) pathways are activated to
20 induce cell proliferation. In the cyst epithelial cells, the
expression of vasopressin receptor (V2R) is enhanced and
adenylate cyclase activity is elevated, which further increases
cAMP levels and accelerates cell proliferation.

Vasopressin receptor antagonists have been reported to
25 have complete response in animal models of polycystic kidney
disease, and tolvaptan is advancing in clinical trials (see, for
example, Patent Literature (PTL) 1 and Non-patent Literature
(NPL) 1, 2, and 3).

Octreotide, which is a somatostatin derivative that
30 suppresses adenylyate cyclase activity, is also expected to be
useful as an agent for treating ADPKD, and clinical test results
therefor have recently been reported (see Non-patent Literature
(NPL) 4).

Citation List

35 Patent Literature

PTL 1: JP4-154765A

Non-patent Literature

NPL 1: Nat. Med., 2003, 9(10):1323-6

NPL 2: J. Am. Soc. Nephrol., 2005, 16:846-851

5 NPL 3: Clin. J. Am. Soc. Nephrol. 2008, 3:1212-1218

NPL 4: J. Am. Soc. Nephrol., 2010, 21:1052-1061

Summary of Invention

Technical Problem

10 An object of the present invention is to provide a combination drug that has remarkably excellent preventive and/or therapeutic effects on polycystic kidney disease.

Solution to Problem

To solve the above problem, the present inventors conducted extensive research on combination drugs that can
15 remarkably increase preventive and/or therapeutic effects on polycystic kidney disease. As a result, the inventors confirmed that the combined use of tolvaptan and a somatostatin derivative, octreotide, can produce remarkable therapeutic effects (e.g., reduction of kidney weight) on polycystic kidney disease,
20 compared to the use of either compound alone. Further, the inventors confirmed that a combination of tolvaptan and the somatostatin derivative can provide remarkable therapeutic effects on polycystic kidney disease, even when the dose of the tolvaptan and/or the somatostatin derivative is so low as to be
25 ineffective if either of the compounds is used alone. As a result of further research based on this finding, the present invention has been accomplished.

More specifically, the present invention provides the following combination drugs.

30 Item 1. A drug for preventing and/or treating polycystic kidney disease comprising a combination of tolvaptan or a prodrug thereof with a somatostatin derivative.

Item 2. The drug according to Item 1 comprising a combination of a pharmaceutical composition (a pharmaceutical
35 preparation) comprising tolvaptan or a prodrug thereof with a

pharmaceutical composition (a pharmaceutical preparation) comprising a somatostatin derivative.

Item 3. The drug according to Item 1 or 2 comprising a low dose of tolavaptan or a prodrug thereof that would be
5 ineffective if used alone.

Item 4. The drug according to any one of Items 1 to 3 wherein the somatostatin derivative is octreotide, pasireotide, lanreotide, vapreotide, or a salt thereof.

Item 5. The drug according to any one of Items 1 to 4
10 which is a combination of an orally administered drug comprising tolavaptan or a prodrug thereof and an injectable preparation comprising a somatostatin derivative.

Item 6. The drug according to Item 5 wherein the injectable preparation comprising the somatostatin derivative is
15 a subcutaneously administered drug.

Item 7. The drug according to Item 5 wherein the injectable preparation comprising the somatostatin derivative is an intramuscularly administered drug.

Item 8. Use of a combination of tolavaptan or a prodrug
20 thereof with a somatostatin derivative in the manufacture of a drug for preventing and/or treating polycystic kidney disease.

Item 9. A drug comprising a combination of tolavaptan or a prodrug thereof with a somatostatin derivative for use in the prevention and/or treatment of polycystic kidney disease.

Item 10. A method for treating polycystic kidney
25 disease, comprising administering tolavaptan or a prodrug thereof in combination with a somatostatin derivative to a polycystic kidney disease patient.

Item 11. The method according to Item 10 wherein the
30 tolavaptan or prodrug thereof is orally administered and the somatostatin derivative is subcutaneously or intramuscularly administered to the polycystic kidney disease patient.

Item 12. A kit for preventing and/or treating polycystic kidney disease comprising an orally administered drug
35 comprising tolavaptan or a prodrug thereof and an injectable

preparation (in particular, a subcutaneously administered drug or an intramuscularly administered drug) comprising a somatostatin derivative.

Item 13. The drug according to any one of Items 1 to 7
5 wherein the tolvaptan or a prodrug thereof is tolvaptan and the somatostatin derivative is octreotide.

Item 14. The use according to Item 8 wherein the tolvaptan or a prodrug thereof is tolvaptan and the somatostatin derivative is octreotide.

10 Item 15. The drug according to Item 9 wherein the tolvaptan or a prodrug thereof is tolvaptan and the somatostatin derivative is octreotide.

Item 16. The method according to Item 10 or 11 wherein the tolvaptan or a prodrug thereof is tolvaptan and the
15 somatostatin derivative is octreotide.

Item 17. The kit according to Item 12 wherein the tolvaptan or a prodrug thereof is tolvaptan and the somatostatin derivative is octreotide.

Advantageous Effects of Invention

20 The drug comprising a combination of tolvaptan or a prodrug thereof with a somatostatin derivative according to the present invention provides remarkable therapeutic effects on polycystic kidney disease (e.g., a kidney weight increase-suppressing effect, a renal function-improving effect, etc.),
25 compared to either compound used alone. A combination of tolvaptan or a prodrug thereof with a somatostatin derivative provides remarkable therapeutic effects on polycystic kidney disease, even when the dose of tolvaptan or a prodrug thereof and/or the somatostatin derivative is so low as to be ineffective
30 if either compound is used alone.

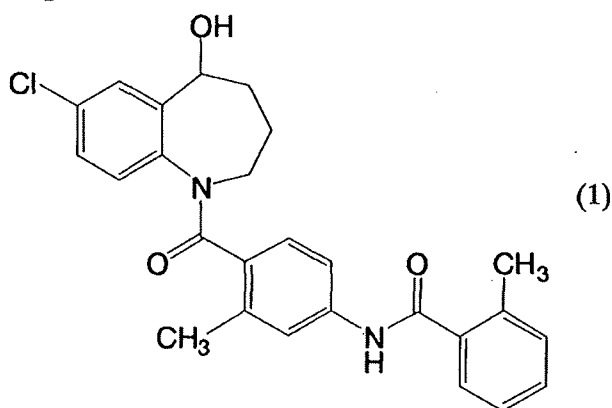
Because the combination drug of the present invention can thereby maintain drug efficacy while reducing side effects, the provision of high therapeutic effects while maintaining the quality of life (QOL) of polycystic kidney disease patients can
35 be expected.

Description of Embodiments

A feature of the drug for preventing and/or treating polycystic kidney disease according to the present invention is that it comprises a combination of tolvaptan or a prodrug thereof
5 with a somatostatin derivative.

1. Tolvaptan and a prodrug thereof

Tolvaptan is the common name for 7-chloro-5-hydroxy-1-[2-methyl-4-(2-methylbenzoylamino)benzoyl]-2,3,4,5-tetrahydro-1H-benzoazepine, represented by Formula (1).



10

Tolvaptan contains a hydroxy-bonded carbon atom as an asymmetric carbon, as shown in Formula (I). Therefore, tolvaptan has a pair of enantiomers (R- and S-enantiomers) based on the asymmetric carbon. The term "tolvaptan" is used to include R
15 enantiomer, S enantiomer, and a mixture of the two enantiomers in any proportion. Tolvaptan is preferably R enantiomer, S enantiomer, or a racemic compound (an equal mixture of R enantiomer and S enantiomer); and is more preferably a racemic compound.

20 Tolvaptan may be crystalline, amorphous, or a mixture of the two. When crystals have two or more polymorphisms, tolvaptan includes all of the polymorphisms.

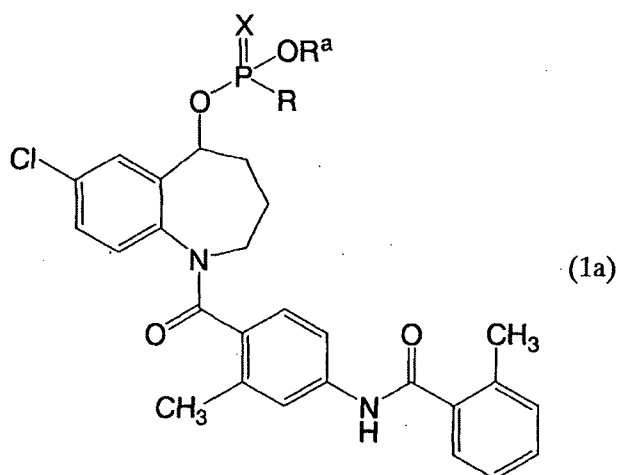
Tolvaptan may be such that one or more atoms in the molecule of the tolvaptan are replaced by one or more isotopes
25 thereof. Examples of such isotopes include deuterium (^2H), tritium (^3H), ^{13}C , ^{14}N , ^{18}O , and the like.

Tolvaptan may be in the form of, for example, an

anhydride, a solvate (e.g., a hydrate, an alcoholate, etc.), a salt, or co-crystals.

Tolvaptan may be a prodrug. The prodrug is a compound obtained by modifying an active compound (tolvaptan) in consideration of improved solubility in water, improved stabilization, improved bioavailability, etc.

An example of a prodrug is a compound produced by phosphorylation of the hydroxy group of tolvaptan. Specific examples thereof include a benzazepine compound represented by the following Formula (1a) or a salt thereof, which is disclosed in JP2009-521397A.



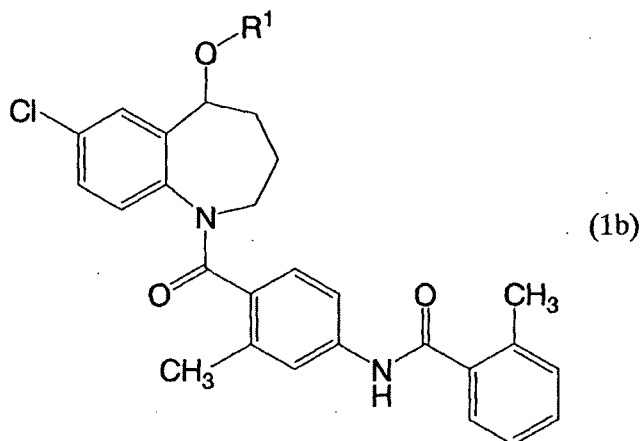
(wherein R is a hydrogen atom, a hydroxy group optionally having a protecting group, a mercapto group optionally having a protecting group, or an amino group optionally having one or two protecting groups; R^a is a hydrogen atom or a hydroxy-protecting group; and X is an oxygen atom or a sulfur atom).

In Formula (1a), there is no particular limitation on the "protecting group" for the hydroxy group optionally having a protecting group, the mercapto group optionally having a protecting group, or the amino group optionally having one or two protecting groups, represented by R. Typical examples of protecting groups include lower alkyl groups (for example, C₁₋₆ alkyl groups, such as methyl and ethyl), phenyl-lower alkyl groups (for example, phenyl-C₁₋₆ alkyl groups, such as benzyl and phenethyl), lower alkoxy carbonyl groups (for example, C₁₋₆

alkoxycarbonyl groups, such as methoxycarbonyl, ethoxycarbonyl, and tert-butoxycarbonyl), and the like.

Examples of the hydroxy protecting group represented by R^a in Formula (1a) are those mentioned above as examples of the "protecting group" included in R.

Other examples of prodrugs include a compound obtained by acylating the hydroxy group of tolvaptan. Specific examples thereof include a benzazepine compound represented by the following formula (1b) or a salt thereof, which are disclosed in WO2009/001968 (JP2010-531293A).



wherein R^1 is a group of (1-1) to (1-7) below:

- (1-1) a $-\text{CO}-(\text{CH}_2)_n-\text{COR}^2$ group
(wherein n is an integer of 1 to 4, R^2 is (2-1) a hydroxy group;
- 15 (2-2) a lower alkoxy group optionally substituted with a hydroxy group, a lower alkanoyl group, a lower alkanoyloxy group, a lower alkoxycarbonyloxy group, a cycloalkyloxycarbonyloxy group, or 5-methyl-2-oxo-1,3-dioxol-4-yl; or (2-3) an amino group optionally substituted with a hydroxy-lower alkyl group);
- 20 (1-2) a $-\text{CO}-(\text{CH}_2)_m-\text{NR}^3\text{R}^4$ group
(wherein m is an integer of 0 to 4, R^3 is a hydrogen atom or a lower alkyl group, R^4 is (4-1) a hydrogen atom; (4-2) a lower alkyl group optionally substituted with a halogen atom, a lower alkylamino group, a lower alkoxycarbonyl group, or 5-methyl-2-oxo-1,3-dioxol-4-yl; or (4-3) a lower alkoxycarbonyl group
- 25 optionally substituted with a halogen atom, a lower alkanoyloxy

- group, or 5-methyl-2-oxo-1,3-dioxol-4-yl, R^3 and R^4 may form a 5- or 6-membered saturated heterocyclic ring by bonding R^3 and R^4 to each other, together with the nitrogen atom to which R^3 and R^4 bond, directly or via a nitrogen atom or oxygen atom, the
- 5 heterocyclic ring being optionally substituted with (4-4) a lower alkyl group (the lower alkyl group being optionally substituted with a hydroxy-lower alkoxy group); (4-5) a lower alkoxycarbonyl group; (4-6) an alkylcarbonyl group (the alkyl group being optionally substituted with a carboxyl group or a lower
- 10 alkoxycarbonyl group); (4-7) an arylcarbonyl group; or (4-8) a furylcarbonyl group);
- (1-3) a $-\text{CO}-(\text{CH}_2)_p-\text{O}-\text{CO}-\text{NR}^5\text{R}^6$ group
(wherein p is an integer of 1 to 4, R^5 is a lower alkyl group, and R^6 is a lower alkoxycarbonyl-lower alkyl group);
- 15 (1-4) a $-\text{CO}-(\text{CH}_2)_q-\text{X}-\text{R}^7$ group
(wherein q is an integer of 1 to 4, X is an oxygen atom, a sulfur atom, or a sulfonyl group, and R^7 is a carboxy-lower alkyl group, or a lower alkoxycarbonyl-lower alkyl group);
- (1-5) a $-\text{CO}-\text{R}^8$ group
- 20 (wherein R^8 is (8-1) an alkyl group optionally substituted with a halogen atom, a lower alkanoyloxy group, or a phenyl group (the phenyl group being substituted with a dihydroxyphosphoryloxy group in which the hydroxy groups are optionally substituted with benzyl groups, and a lower alkyl group), (8-2) a lower alkoxy
- 25 group substituted with a halogen atom, a lower alkanoyloxy group, or a dihydroxyphosphoryloxy group, (8-3) a pyridyl group, or (8-4) a lower alkoxyphenyl group);
- (1-6) a lower alkyl group substituted with a group selected from the group consisting of lower alkylthio groups, a
- 30 dihydroxyphosphoryloxy group, and lower alkanoyloxy groups; and (1-7) an amino acid or peptide residue optionally protected with one or more protecting groups.

In Formula (1b), the term "lower" refers to " C_{1-6} ", unless otherwise specified.

35 Examples of lower alkanoyl groups include straight or

branched C₂₋₆ alkanoyl groups, such as acetyl, n-propionyl, n-butyryl, isobutyryl, n-pentanoyl, tert-butylcarbonyl, and n-hexanoyl.

Examples of lower alkanoyloxy groups include straight
5 or branched C₂₋₆ alkanoyloxy groups, such as acetyloxy, n-propionyloxy, n-butyryloxy, isobutyryloxy, n-pentanoyloxy, tert-butylcarbonyloxy, and n-hexanoyloxy.

Examples of lower alkoxy carbonyloxy groups include
alkoxy carbonyloxy groups in which the alkoxy moiety is a straight
10 or branched C₁₋₆ alkoxy group, such as methoxy carbonyloxy, ethoxy carbonyloxy, n-propoxy carbonyloxy, isopropoxy carbonyloxy, n-butoxy carbonyloxy, isobutoxy carbonyloxy, tert-butoxy carbonyloxy, sec-butoxy carbonyloxy, n-pentyloxy carbonyloxy, neopentyloxy carbonyloxy, n-
15 hexyloxy carbonyloxy, isohexyloxy carbonyloxy, and 3-methyl pentyloxy carbonyloxy.

Examples of cycloalkyloxy carbonyloxy groups include
cycloalkyloxy carbonyloxy groups in which the cycloalkyl moiety is
a C₃₋₈ cycloalkyl group, such as cyclopropyloxy carbonyloxy,
20 cyclobutyloxy carbonyloxy, cyclopentyloxy carbonyloxy, cyclohexyloxy carbonyloxy, cycloheptyloxy carbonyloxy, and cyclooctyloxy carbonyloxy.

Examples of cycloalkyl carbonyl groups include
cycloalkyl carbonyl groups in which the cycloalkyl moiety is a C₃₋₈
25 cycloalkyl group, such as cyclopropyl carbonyl, cyclobutyl carbonyl, cyclopentyl carbonyl, cyclohexyl carbonyl, cycloheptyl carbonyl, and cyclooctyl carbonyl.

Examples of lower alkoxy groups include straight or
branched C₁₋₆ alkoxy groups, such as methoxy, ethoxy, n-propoxy,
30 isopropoxy, n-butoxy, isobutoxy, tert-butoxy, sec-butoxy, n-pentyloxy, isopentyloxy, neopentyloxy, n-hexyloxy, isohexyloxy, and 3-methylpentyloxy.

Examples of hydroxy-lower alkyl groups include straight
or branched C₁₋₆ alkyl groups having one to three hydroxy groups,
35 such as hydroxymethyl, 2-hydroxyethyl, 1-hydroxyethyl, 3-

hydroxypropyl, 2,3-dihydroxypropyl, 4-hydroxybutyl, 3,4-dihydroxybutyl, 1,1-dimethyl-2-hydroxyethyl, 5-hydroxypentyl, 6-hydroxyhexyl, 3,3-dimethyl-3-hydroxypropyl, 2-methyl-3-hydroxypropyl, and 2,3,4-trihydroxybutyl.

5 Examples of alkyl groups include straight or branched C₁₋₁₀ alkyl groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, isohexyl, and 3-methylpentyl.

10 Examples of lower alkyl groups include straight or branched C₁₋₆ alkyl groups, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, tert-butyl, sec-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, isohexyl, and 3-methylpentyl.

 Examples of halogen atoms include fluorine, chlorine, bromine, and iodine.

15 Examples of lower alkylamino groups include amino groups substituted with one to two straight or branched C₁₋₆ alkyl groups, such as methylamino, ethylamino, n-propylamino, isopropylamino, n-butylamino, tert-butylamino, n-pentylamino, n-hexylamino, dimethylamino, diethylamino, di-n-propylamino, di-n-butylamino, di-n-pentylamino, di-n-hexylamino, N-methyl-N-ethylamino, N-ethyl-N-n-propylamino, N-methyl-N-n-butylamino, and N-methyl-N-n-hexylamino.

25 Examples of lower alkoxy carbonyl groups include alkoxy carbonyl groups in which the alkoxy moiety is a straight or branched C₁₋₆ alkoxy group, such as methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl, isobutoxycarbonyl, tert-butoxycarbonyl, sec-butoxycarbonyl, n-pentyloxycarbonyl, neopentyloxycarbonyl, n-hexyloxycarbonyl, isohexyloxycarbonyl, and 3-methylpentyloxycarbonyl.

30 Examples of 5- or 6-membered saturated heterocyclic rings formed by bonding R³ and R⁴ to each other, together with the nitrogen atom to which R³ and R⁴ bond, directly or via a nitrogen atom or oxygen atom include pyrrolidine, imidazolidine, piperazine, piperidine, and morpholine.

Examples of hydroxy-lower alkoxy groups include hydroxyalkoxy groups that have one or two hydroxy groups, the alkoxy moiety being a straight or branched C₁₋₆ alkoxy group, such as hydroxymethoxy, 2-hydroxyethoxy, 1-hydroxyethoxy, 3-
5 hydroxypropoxy, 4-hydroxybutoxy, 5-hydroxypentyloxy, 6-hydroxyhexyloxy, 1,1-dimethyl-2-hydroxyethoxy, and 2-methyl-3-hydroxypropoxy.

Examples of alkylcarbonyl groups include alkylcarbonyl groups in which the alkyl moiety is a straight or branched C₁₋₂₀
10 alkyl group, such as methylcarbonyl, ethylcarbonyl, n-propylcarbonyl, isopropylcarbonyl, n-butylcarbonyl, isobutylcarbonyl, tert-butylcarbonyl, sec-butylcarbonyl, n-pentylcarbonyl, isopentylcarbonyl, neopentylcarbonyl, n-hexylcarbonyl, isohexylcarbonyl, 3-methylpentylcarbonyl, n-
15 heptylcarbonyl, n-octylcarbonyl, n-nonylcarbonyl, n-decylcarbonyl, n-undecylcarbonyl, n-dodecylcarbonyl, n-tridecylcarbonyl, n-tetradecylcarbonyl, n-pentadecylcarbonyl, n-hexadecylcarbonyl, n-heptadecylcarbonyl, n-octadecylcarbonyl, n-nonadecylcarbonyl, and n-icosylcarbonyl.

20 Examples of arylcarbonyl groups include phenylcarbonyl and (1- or 2-)naphthylcarbonyl.

Examples of furylcarbonyl groups include (2- or 3-)furylcarbonyl.

Examples of lower alkoxy carbonyl-lower alkyl groups
25 include alkoxy carbonyl alkyl groups in which the alkoxy moiety is a straight or branched C₁₋₆ alkoxy group, and the alkyl moiety is a straight or branched C₁₋₆ alkyl group, such as methoxycarbonylmethyl, ethoxycarbonylmethyl, 2-methoxycarbonylethyl, 2-ethoxycarbonylethyl, 1-
30 ethoxycarbonylethyl, 3-methoxycarbonylpropyl, 3-ethoxycarbonylpropyl, 4-ethoxycarbonylbutyl, 5-isopropoxycarbonyl pentyl, 6-n-propoxycarbonylhexyl, 1,1-dimethyl-2-n-butoxycarbonylethyl, 2-methyl-3-tert-butoxycarbonylpropyl, 2-n-pentyloxycarbonylethyl, and n-hexyloxycarbonylmethyl.

35 Examples of carboxy-lower alkyl groups include

carboxyalkyl groups in which the alkyl moiety is a straight or branched C₁₋₆ alkyl group, such as carboxymethyl, 2-carboxyethyl, 1-carboxyethyl, 3-carboxypropyl, 4-carboxybutyl, 5-carboxypentyl, 6-carboxyhexyl, 1,1-dimethyl-2-carboxyethyl, and 2-methyl-3-carboxypropyl.

Examples of lower alkoxyphenyl groups include alkoxyphenyl groups in which the alkoxy moiety is a straight or branched C₁₋₆ alkoxy group, such as methoxyphenyl, ethoxyphenyl, n-propoxyphenyl, isopropoxyphenyl, n-butoxyphenyl, isobutoxyphenyl, tert-butoxyphenyl, sec-butoxyphenyl, n-pentyloxyphenyl, isopentyloxyphenyl, neopentyloxyphenyl, n-hexyloxyphenyl, isohexyloxyphenyl, and 3-methylpentyloxyphenyl.

Examples of lower alkylthio groups include straight or branched C₁₋₆ alkylthio groups, such as methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, tert-butylthio, n-pentylthio, and n-hexylthio.

Examples of amino acid or peptide residues include amino acid residues such as alanyl, phenylalanyl, sarcosyl, valyl, leucyl, isoleucyl, prolyl, N-ethylglycyl, N-propylglycyl, N-isopropylglycyl, N-butylglycyl, N-tert-butylglycyl, N-pentylglycyl, N-hexylglycyl, N,N-diethylglycyl, N,N-dipropylglycyl, N,N-dibutylglycyl, N,N-dipentylglycyl, N,N-diethylglycyl, N-methyl-N-ethylglycyl, N-methyl-N-propylglycyl, N-methyl-N-butylglycyl, N-methyl-N-pentylglycyl, and N-methyl-N-hexylglycyl; and peptide residues such as sarcosyl-glycyl, glycyl-glycyl, glycyl-sarcosyl, sarcosyl-sarcosyl, alanyl-glycyl, phenylalanyl-glycyl, phenylalanyl-phenylalanyl, glycyl-glycyl-glycyl, N-ethylglycyl-glycyl, N-propylglycyl-glycyl, N,N-dimethylglycyl-glycyl, N,N-diethylglycyl-glycyl, N-methyl-N-ethylglycyl-glycyl, sarcosyl-glycyl-glycyl, N-ethylglycyl-glycyl-glycyl, and N,N-dimethylglycyl-glycyl-glycyl.

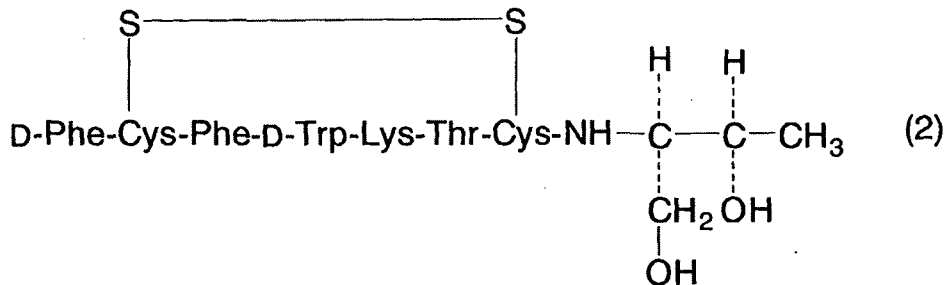
Examples of protecting groups for amino acids or peptides include those usually used to protect amino groups of amino acids or peptides, such as tert-butoxycarbonyl, benzyloxycarbonyl, fluorenylmethoxycarbonyl, and acetyl.

In this specification, a prodrug of tolgevaptan (in particular, a compound of Formula (1a) and/or a compound of Formula (1b)) can be used together with or substituted for tolgevaptan. In the present invention, tolgevaptan is preferable.

5 2. Somatostatin derivative

The term "somatostatin derivative" refers to somatostatin, a compound comprising an amino acid sequence (Phe-Trp-Lys-Thr) essential for the physiological activity of somatostatin; or salts thereof. Specific examples thereof include
 10 somatostatin, octreotide, pasireotide, lanreotide, vapreotide, and the like. Such compounds can be used singly, or in a combination of two or more. Octreotide is preferable.

Octreotide refers to a cyclic polypeptide represented by Formula (2), and is the common name for (-)-D-phenylalanyl-L-cysteinyl-L-phenylalanyl-D-tryptophyl-L-lysyl-L-threonyl-N-
 15 [(1R,2R)-2-hydroxy-1-(hydroxymethyl)propyl]-L-cysteinamide cyclic (2→7) disulfide.



The somatostatin derivative may form a salt with a pharmaceutically acceptable acid. Examples of such acids include
 20 inorganic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, and phosphoric acid; and organic acids such as methanesulfonic acid, p-toluenesulfonic acid, acetic acid, citric acid, tartaric acid, maleic acid, fumaric acid, malic acid, and lactic acid. The salt of the somatostatin
 25 derivative is preferably hydrochloride or acetate, and more preferably diacetate of octreotide. This is commercially available under the trade name "Sandostatin" (a product of Novartis Pharma K.K.).

3. Pharmaceutical preparation

A feature of the drug for preventing and/or treating polycystic kidney disease according to the present invention is that it comprises a combination of tolvaptan or a prodrug thereof with a somatostatin derivative. The combination is preferably a
5 combination of tolvaptan with a somatostatin derivative. A combination of tolvaptan with octreotide, a combination of tolvaptan with pasireotide, a combination of tolvaptan with lanreotide, or a combination of tolvaptan with vapreotide is more preferable. A combination of tolvaptan with octreotide is even
10 more preferable. These combinations apply to the entire invention.

The drug of the present invention may be in the form of a single formulation (a mixture) comprising tolvaptan or a prodrug thereof with a somatostatin derivative; or in the form of separate formulations (concomitants), one of the formulations
15 comprising tolvaptan or a salt thereof, and the other comprising a somatostatin derivative. The drug is preferably concomitants.

One example of such concomitants is a combination of a pharmaceutical composition (a pharmaceutical preparation) comprising tolvaptan or a prodrug thereof with a pharmaceutical
20 composition (a pharmaceutical preparation) comprising a somatostatin derivative.

The pharmaceutical preparation comprising a combination of tolvaptan or a prodrug thereof with a somatostatin derivative may be a mixture or concomitants, and the dosage form of the
25 pharmaceutical preparation can be suitably selected from those described below.

The pharmaceutical preparation can be produced by incorporating tolvaptan or a prodrug thereof and/or a somatostatin derivative by a conventional method using a commonly
30 used diluent and/or excipient, such as a filler, an extender, a binder, a humectant, a disintegrator, a surfactant, and a lubricant.

The form of the pharmaceutical preparation can be suitably selected from various forms according to the therapeutic
35 purpose. Typical examples of such forms include tablets, pills,

powders, liquids, suspensions, emulsions, granules, capsules, suppositories, ointments, injections (solutions, suspensions, emulsions, etc.), and the like.

To form tablets, various carriers known in the art can be used. Examples of such carriers include excipients such as lactose, sucrose, sodium chloride, glucose, urea, starch, calcium carbonate, kaolin, and crystalline cellulose; binders such as water, ethanol, propanol, simple syrup, glucose solution, starch solution, gelatin solution, carboxymethyl cellulose, shellac, methylcellulose, potassium phosphate, and polyvinylpyrrolidone; disintegrators such as dry starch, sodium alginate, agar powder, laminaran powder, sodium hydrogen carbonate, calcium carbonate, polyoxyethylene sorbitan fatty acid esters, sodium lauryl sulfate, stearic acid monoglyceride, starch, and lactose; disintegration inhibitors such as sucrose, stearin, cacao butter, and hydrogenated oil; absorption promoters such as quaternary ammonium salts and sodium lauryl sulfate; humectants such as glycerol and starch; adsorbents such as starch, lactose, kaolin, bentonite, and colloidal silica; and lubricants such as purified talc, stearic acid salts, boric acid powder, and polyethylene glycol.

The tablets, if desired, can be coated with a general coating material to give coated tablets. Examples of such coated tablets include sugar-coated tablets, gelatin-coated tablets, enteric coated tablets, film-coated tablets, bilayer tablets, and multilayer tablets.

To form pills, various carriers known in the art can be used. Examples of such carriers include excipients such as glucose, lactose, starch, cacao butter, hydrogenated vegetable oil, kaolin, and talc; binders such as gum arabic powder, tragacanth powder, gelatin, and ethanol; and disintegrants such as laminaran and agar.

To form suppositories, various carriers known in the art can be used. Examples of such carriers include polyethylene glycol, cacao butter, higher alcohols, higher alcohol esters,

gelatin, and semisynthetic glycerides.

5 Injections are preferably prepared in the form of
solutions, emulsions, or suspensions that are sterilized and
isotonic with blood. To form such solutions, emulsions, and
10 suspensions using tolvaptan or a prodrug thereof and/or a
somatostatin derivative, any diluents commonly used in the art
can be used. Examples of such diluents include water, lactic acid
aqueous solution, ethanol, propylene glycol, ethoxylated
isostearyl alcohol, polyoxylated isostearyl alcohol, and
15 polyoxyethylene sorbitan fatty acid ester. In this case, an
isotonizing agent, such as sodium chloride, glucose, mannitol, or
glycerol, may be incorporated into such a pharmaceutical
preparation in an amount sufficient for making the preparation
isotonic. Further, commonly used pH adjusters, solubilizers,
20 buffers, soothing agents, etc., as well as coloring agents,
preservatives, flavors, sweetening agents, and/or other medicines
may be added, if necessary.

 The amount of tolvaptan or a prodrug thereof and/or
somatostatin derivative in the pharmaceutical preparation of the
25 invention is not particularly limited insofar as it is a
therapeutically effective amount as a combination drug, and can
be suitably selected from a wide range. It is generally
preferable that tolvaptan or a prodrug thereof and/or a
somatostatin derivative are contained in the pharmaceutical
30 preparation in a proportion of about 0.01 to about 70 wt%. For
example, when concomitants are used as the combination drug, the
pharmaceutical preparation comprising tolvaptan or a prodrug
thereof typically comprises the tolvaptan or the prodrug thereof
in an amount of 0.01 to 70 wt.%, and the pharmaceutical
35 preparation comprising a somatostatin derivative typically
comprises the somatostatin derivative in an amount of 0.01 to 70
wt.%.

4. Administration method and dosage

 The method of administration (administration route) of
35 the pharmaceutical preparation of the invention is not

particularly limited. This preparation can be administered by a method suitable for the dosage form, the patient's age and sex, the status of the disease, and other conditions. For example, tablets, pills, liquids, suspensions, emulsions, granules, and capsules are administered orally. Injections are intravenously administered singly or as a mixture with a general injection transfusion, such as glucose solution or amino acid solution, or singly administered intramuscularly, intracutaneously, subcutaneously or intraperitoneally, as required. The suppositories are administered intrarectally.

Typical examples of the combination drug of the present invention are concomitants. One example of such concomitants is a combination of a pharmaceutical composition (a pharmaceutical preparation) comprising tolvaptan or a prodrug thereof with a pharmaceutical composition (a pharmaceutical preparation) comprising a somatostatin derivative. In this case, the pharmaceutical preparation comprising tolvaptan or a prodrug thereof may be, for example, an orally administered drug (an oral preparation), an intramuscularly administered drug (a sustained-release preparation), or an intravenously administered drug (a sustained-release preparation); the pharmaceutical preparation is preferably an oral preparation. The pharmaceutical preparation comprising a somatostatin derivative may be, for example, a subcutaneously administered drug (a subcutaneous injection), an intramuscularly administered drug (a sustained-release preparation), or an orally administered drug (an oral preparation), and is preferably a subcutaneously administered drug.

Examples of the combination of concomitants include, but are not limited to, a combination of an orally administered drug comprising tolvaptan or a prodrug thereof and a subcutaneously administered drug comprising a somatostatin derivative, and a combination of one drug comprising tolvaptan or a prodrug thereof and another drug comprising a somatostatin derivative, both being subcutaneously administered drugs

(subcutaneous injections).

The dose of the combination drug of the present invention is suitably selected according to the dosage regimen, the patient's age and sex, the severity of the disease, and other
5 conditions.

The dosage regimen of the pharmaceutical preparation comprising tolvaptan or a prodrug thereof is usually such that tolvaptan or a prodrug thereof is administered in an amount of about 0.001 to 300 mg, preferably 0.001 to 100 mg, per kg (body
10 weight) per day in one or more administrations.

Even when tolvaptan or a prodrug thereof is administered in a low dose that would be ineffective if used alone, a combination thereof with a somatostatin derivative can provide excellent therapeutic effects on polycystic kidney
15 disease. The dosage regimen of the pharmaceutical preparation comprising tolvaptan or a prodrug thereof when used in combination with a somatostatin derivative is such that tolvaptan or a prodrug thereof is administered in an amount of about 0.001 to 50 mg, and preferably 0.001 to 30 mg, per kg (body weight) per
20 day in one or more administrations.

The dosage regimen of the preparation comprising a somatostatin derivative is usually such that the somatostatin derivative is administered in an amount of about 0.001 to 10 mg, preferably 0.001 to 1 mg, per kg (body weight) per day in one or
25 more administrations.

The pharmaceutical preparation comprising tolvaptan or a prodrug thereof with the pharmaceutical preparation comprising a somatostatin derivative can be administered to a human (in particular, a patient) simultaneously or with a delay between
30 administrations.

The present invention includes use of a combination of tolvaptan or a prodrug thereof with a somatostatin derivative in the manufacture of a drug for preventing and/or treating polycystic kidney disease.

35 The present invention includes a combination drug of

tolvaptan or a prodrug thereof and a somatostatin derivative for use in the prevention and/or treatment of polycystic kidney disease.

5 The present invention includes a method for treating polycystic kidney disease, comprising administering a combination of tolvaptan or a prodrug thereof with a somatostatin derivative to a polycystic kidney disease patient. Preferable dosage forms are such that tolvaptan is administered orally and a somatostatin derivative is administered subcutaneously or intramuscularly.

10 The present invention includes a kit for preventing and/or treating polycystic kidney disease comprising an orally administered drug comprising tolvaptan or a prodrug thereof and an injectable preparation (in particular, a subcutaneously administered drug or an intramuscularly administered drug)
15 comprising a somatostatin derivative. Examples of the kit include a kit comprising a container containing an orally administered drug comprising tolvaptan or a prodrug thereof and a container containing a subcutaneously administered drug or an intramuscularly administered drug comprising a somatostatin
20 derivative.

 The entire contents and disclosures of each patent and reference disclosed herein are incorporated by reference.

Examples

 The present invention will now be illustrated with the
25 following examples. However, the invention is not limited thereto or thereby.

Example 1

 Individual or combined effects of tolvaptan, which is a vasopressin receptor antagonist, and octreotide, which is a
30 somatostatin analogue, against polycystic kidney disease were evaluated using pcy mice, which are PKD model animals.

 The aforementioned pcy mice are adult polycystic kidney disease model mice, and the mode of inheritance is autosomal recessive. In DBA/2FG-pcy mice generated by introducing the pcy
35 gene into DBA/2 mice, cysts were observed with the naked eye from

the fourth week, and the kidney volume increased over time until the 30th week. It has been reported that compared to wild-type mice, pcy mice have increased renal cAMP levels and elevated renal mRNA levels of aquaporin-2 and vasopressin V2 receptor (V2R). For details, see Non-patent Literature (NPL) 1.

Based on the body weight at 4 weeks of age and the renal volume measured by MRI, the pcy mice (male) were divided into the following four groups (each group: 9 mice):

- (1) a control group;
- 10 (2) a group receiving a feed containing 0.03% tolvaptan;
- (3) a group receiving octreotide (300 µg/kg x 2/day sc); and
- (4) a group receiving a feed containing 0.03% tolvaptan, and octreotide (300 µg/kg x 2/day sc).

As normal control mice, DBA/2JJcl mice (5 mice) were used. A 0.03% tolvaptan-containing MF feed was given to the groups receiving tolvaptan. A MF feed not containing tolvaptan was given to the other groups, i.e., the control group and the group receiving octreotide alone. Sandostatin subcutaneous injection (100 µg/ml) was diluted with physiological saline and subcutaneously injected in an amount of 300 µg/kg/10 ml to the group receiving octreotide twice a day, morning and evening.

The drug treatment was started from 5 weeks of age, and continued until 15 weeks of age. Urine was collected from each mouse at 14 weeks of age using metabolic cages for 19 hours, and urine volume and urinary albumin excretion were measured.

The DBA control mice and pcy mice were sacrificed under isoflurane anesthesia at 15 weeks of age to collect their blood, and right and left kidneys. Plasma parameters were measured from the obtained blood, and the weight of right and left kidneys was measured.

Table 1 shows the weight of the kidneys (% body weight) during autopsy. At 15 weeks of age, marked renal hypertrophy and cysts were observed in pcy control mice, compared to normal DBA mice. The kidney weight was increased 5.2-fold. Compared to the pcy control group, the group receiving 0.03% tolvaptan-containing

feed and the group subcutaneously receiving octreotide did not exhibit significant kidney weight suppressive effects when either tolvaptan or octreotide was administered alone. In contrast, a significant kidney weight suppressive effect was observed in the group receiving both tolvaptan and octreotide ($p < 0.01$), compared to the pcy control. The group receiving both tolvaptan and octreotide exhibited a significantly high kidney weight suppressive effect ($p < 0.05$), compared to the groups receiving either tolvaptan or octreotide alone.

Table 1

Kidney weight of (15-week-old) pcy mice
(body weight adjustment: %)

Group of mice	Number of mice	Kidney weight (% body weight)	Assay results	
		Mean $\pm$ SE	Comparison with the control group	Comparison with the group receiving both of tolvaptan and octreotide
1 Normal DBA	5	1.53 $\pm$ 0.04	-	-
2 Pcy control	9	8.02 $\pm$ 0.66	-	-
3 Pcy receiving 0.03% tolvaptan-containing feed alone	9	7.28 $\pm$ 0.84	NS	$p < 0.05$
4 Pcy receiving octreotide alone (300 μ g/kg x 2/day sc)	9	6.68 $\pm$ 0.65	NS	$p < 0.05$
5 Pcy receiving both 0.03% tolvaptan-containing feed and octreotide (300 μ g/kg x 2/day sc)	9	4.87 $\pm$ 0.36	$p < 0.01$	-

Each value indicates the average value $\pm$ SEM.

For comparison with the control group, Dunnett's test (both sides) was used.

For comparison of the group receiving both of tolvaptan and octreotide with the groups receiving either one of tolvaptan and octreotide, the closed testing procedure was used.

"NS" indicates non-significant.

The above results show that a combination of tolvaptan with octreotide can synergistically suppress cystic kidney enlargement and improve kidney functions.

CLAIMS

[Claim 1]

A drug for preventing and/or treating polycystic kidney disease comprising a combination of tolvaptan or a prodrug thereof with a somatostatin derivative wherein the prodrug is represented by a compound produced by phosphorylation or acylation of the hydroxy group of tolvaptan and wherein the somatostatin derivative is represented by any one, or a combination of two or more, of somatostatin, octreotide, pasireotide, lanreotide and vapreotide, or salts thereof.

[Claim 2]

The drug according to claim 1 comprising a low dose of tolvaptan or a prodrug as defined in claim 1 that would be ineffective if used alone.

[Claim 3]

The drug according to claim 1 or 2 wherein the somatostatin derivative is octreotide, pasireotide, lanreotide, vapreotide, or a salt thereof.

[Claim 4]

A combination drug for preventing and/or treating polycystic kidney disease comprising an orally administered drug containing tolvaptan or a prodrug thereof and an injectable preparation comprising a somatostatin derivative, wherein the prodrug is a compound produced by phosphorylation or acylation of the hydroxy group of tolvaptan and the somatostatin derivative is represented by any one, or a combination of two or more, of somatostatin, octreotide, pasireotide, lanreotide and vapreotide, or salts thereof.

[Claim 5]

The combination drug according to claim 4 comprising a low dose of tolvaptan or the prodrug as defined in claim 4 that would be ineffective if used alone.

[Claim 6]

The combination drug according to claim 4 or 5 wherein the somatostatin derivative is octreotide, pasireotide, lanreotide, vapreotide, or a salt thereof.

[Claim 7]

The combination drug according to any one of claims 4 to 6 wherein the injectable preparation comprising the somatostatin derivative as defined in claim 4 is a subcutaneously administered drug.

[Claim 8]

The combination drug according to any one of claims 4 to 6 wherein the injectable preparation comprising the somatostatin derivative as defined in claim 4 is an intramuscularly administered drug.

[Claim 9]

A drug comprising a combination of tolvaptan or a prodrug thereof with a somatostatin derivative wherein the prodrug is a compound produced by phosphorylation or acylation of the hydroxy group of tolvaptan and the somatostatin derivative is represented by any one, or a combination of two or more, of somatostatin, octreotide, pasireotide, lanreotide and vapreotide, or salts thereof for use in the prevention and/or treatment of polycystic kidney disease.

[Claim 10]

A kit for preventing and/or treating polycystic kidney disease comprising an orally administered drug comprising tolvaptan or a prodrug thereof and an injectable preparation comprising a

somatostatin derivative wherein the prodrug is a compound produced by phosphorylation or acylation of the hydroxy group of tolvaptan and the somatostatin derivative is represented by any one, or a combination of two or more, of somatostatin, octreotide, pasireotide, lanreotide and vapreotide, or salts thereof.