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Description

[Title of Invention] COMPOSITION

[Technical Field]

[0001]

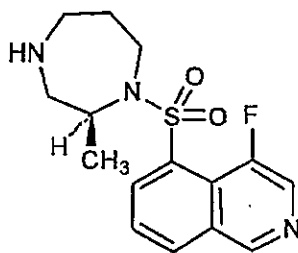
The present invention relates to an aqueous composition and the like.

[Background Art]

[0002]

It is known that halogenated isoquinoline derivatives such as ripasudil (chemical name: 4-fluoro-5-[[(2S)-2-methyl-1,4-diazepan-1-yl]sulfonyl]isoquinoline) represented by the following structural formula:

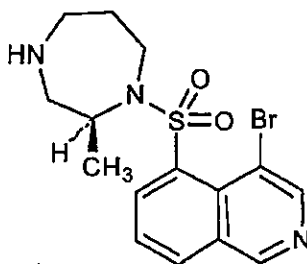
[0003]



[0004]

and 4-bromo-5-[[(2S)-2-methyl-1,4-diazepan-1-yl]sulfonyl]isoquinoline represented by the following structural formula:

[0005]



[0006]

have pharmacological action such as Rho kinase inhibitory action (Patent Literatures 1 and 2, for example), and thus, are usable for the prevention or treatment of eye diseases. Specifically, these halogenated isoquinoline derivatives have been reported to be useful, for example, for the prevention or treatment of ocular hypertension, glaucoma, and the like (Patent Literature 3, for example), or for the prevention or treatment of ocular fundus diseases such as age-related macular degeneration and the like (Patent Literature 4, for example).

[0007]

Hence, it is extremely useful to establish a technique for producing stable preparations of these halogenated isoquinoline derivatives as ophthalmic agents, for example.

[0008]

Patent Literature 5 describes a combination of ripasudil ((S)-(-)-1-(4-fluoro-5-isoquinolinesulfonyl)-2-methyl-1,4-homopiperazine) or a salt thereof or a solvate of ripasudil or the salt thereof, and a prostaglandin such as latanoprost. However, Patent Literature 5 only

discloses that a solution containing 0.4% ripasudil and an eye drop containing 0.05% latanoprost were sequentially instilled in one eye of a cynomolgus monkey, and an aqueous composition containing both of these components, storing the same in a container, and the preservation stability over time, etc., are not disclosed at all.

[Citation List]

[Patent Literature]

[0009]

[Patent Literature 1] JP-B-4212149

[Patent Literature 2] WO2006/115244

[Patent Literature 3] WO2006/068208

[Patent Literature 4] JP-B-5557408

[Patent Literature 5] WO2012/105674

[Summary of the Invention]

[Technical Problem]

[0010]

An ophthalmic agent is generally a composition containing water (aqueous composition). To produce a preparation of a halogenated isoquinoline derivative, ripasudil, as an ophthalmic agent or the like, the present inventor initially prepared an aqueous composition containing ripasudil and the preservation stability was investigated, and as a result the aqueous

composition was revealed to be disadvantageously discolored over time due to high-temperature preservation.

Accordingly, it is an object of the present invention to provide a technique for reducing the discoloration of an aqueous composition containing a halogenated isoquinoline derivative during high-temperature preservation.

[Solution to Problem]

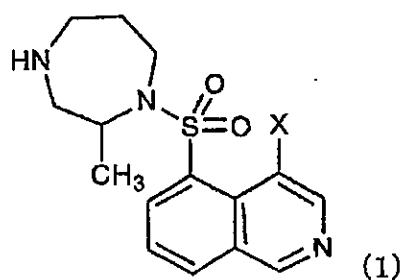
[0011]

Thus, the present inventors conducted extensive research to solve the above-described problem, and found that further incorporation of a prostaglandin such as bimatoprost and latanoprost in an aqueous composition containing a halogenated isoquinoline derivative such as ripasudil can reduce the discoloration during high-temperature preservation, thus completing the present invention.

[0012]

In summary, the present invention provides an aqueous composition comprising a compound represented by Formula (1):

[0013]



[0014]

wherein X represents a halogen atom,
or a salt thereof, or a solvate of the compound or
the salt thereof, and a prostaglandin.

Further, the present invention provides a method for
reducing discoloration of an aqueous composition, the
method comprising the step of incorporating a
prostaglandin in an aqueous composition comprising a
compound represented by Formula (1) or a salt thereof, or
a solvate of the compound or the salt thereof.

[Effects of Invention]

[0015]

In accordance with the present invention, the
discoloration of an aqueous composition containing a
halogenated isoquinoline derivative such as ripasudil
during high-temperature preservation can be reduced.

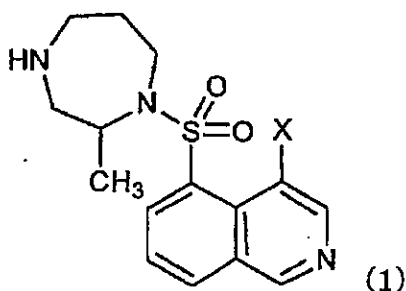
[Description of Embodiments]

[0016]

The present specification discloses, although is in no way limited to, the following embodiments of invention, by way of example.

[1] An aqueous composition comprising a compound represented by Formula (1):

[0017]



[0018]

wherein X represents a halogen atom,
or a salt thereof, or a solvate of the compound or
the salt thereof, and a prostaglandin.

[2] The aqueous composition according to [1],
wherein the compound represented by Formula (1) is
ripasudil.

[3] The aqueous composition according to [1] or [2],
wherein the prostaglandin is one or more selected from
the group consisting of isopropyl unoprostone, tafluprost,
travoprost, bimatoprost, latanoprost, and salts thereof,
as well as solvates thereof.

[4] The aqueous composition according to [1] or [2],
wherein the prostaglandin is one or more selected from
the group consisting of tafluprost, travoprost,

bimatoprost, latanoprost, and salts thereof, as well as solvates thereof.

[5] The aqueous composition according to any of [1] to [4], being an ophthalmic agent.

[6] The aqueous composition according to [5], being an eye drop.

[7] The aqueous composition according to any of [1] to [6], being a prophylactic and/or therapeutic agent for a disease selected from the group consisting of ocular hypertension, glaucoma, and ocular fundus diseases.

[0019]

[8] The aqueous composition according to any of [1] to [7], further containing one or more selected from the group consisting of $\alpha 1$ receptor blockers, $\alpha 2$ receptor agonists, β blockers, carbonic anhydrase inhibitors, sympathomimetics, parasympathomimetics, calcium antagonists, and cholinesterase inhibitors.

[9] The aqueous composition according to any of [1] to [7], further containing one or more selected from the group consisting of nipradilol, dorzolamide, brinzolamide, timolol, a salt of nipradilol, a salt of dorzolamide, a salt of brinzolamide, a salt of timolol, a solvate of nipradilol or the salt thereof, a solvate of dorzolamide or the salt thereof, a solvate of brinzolamide or the salt thereof, and a solvate of timolol or the salt thereof.

[0020]

[10] A pharmaceutical preparation obtained by housing the aqueous composition according to any of [1] to [9] in a container made of polyolefin-based resin.

[11] The pharmaceutical preparation according to [10], wherein the polyolefin-based resin is polyethylene or polypropylene.

[12] The pharmaceutical preparation according to [10] or [11], wherein the container made of polyolefin-based resin is a container for eye drops.

[0021]

[13] A method for reducing discoloration of an aqueous composition, the method comprising the step of incorporating a prostaglandin in an aqueous composition comprising a compound represented by Formula (1) or a salt thereof, or a solvate of the compound or the salt thereof.

[14] The method according to [13], wherein the compound represented by Formula (1) is ripasudil.

[15] The method according to [13] or [14], wherein the prostaglandin is one or more selected from the group consisting of isopropyl unoprostone, tafluprost, travoprost, bimatoprost, latanoprost, a salt of isopropyl unoprostone, a salt of tafluprost, a salt of travoprost, a salt of bimatoprost, a salt of latanoprost, a solvate of isopropyl unoprostone or the salt thereof, a solvate of tafluprost or the salt thereof, a solvate of travoprost or the salt thereof, a solvate of bimatoprost

or the salt thereof, and a solvate of latanoprost or the salt thereof.

[16] The method according to [13] or [14], wherein the prostaglandin is one or more selected from the group consisting of tafluprost, travoprost, bimatoprost, latanoprost, a salt of tafluprost, a salt of travoprost, a salt of bimatoprost, a salt of latanoprost, a solvate of tafluprost or the salt thereof, a solvate of travoprost or the salt thereof, a solvate of bimatoprost or the salt thereof, and a solvate of latanoprost or the salt thereof.

[17] The method according to any of [13] to [16], wherein the aqueous composition is an ophthalmic agent.

[18] The method according to [17], wherein the ophthalmic agent is an eye drop.

[19] The method according to any of [13] to [18], wherein the aqueous composition is a prophylactic and/or therapeutic agent for a disease selected from the group consisting of ocular hypertension, glaucoma, and ocular fundus diseases.

[0022]

[20] The method according to any of [13] to [19], wherein the aqueous composition further contains one or more selected from the group consisting of $\alpha 1$ receptor blockers, $\alpha 2$ receptor agonists, β blockers, carbonic anhydrase inhibitors, sympathomimetics, parasympathomimetics, calcium antagonists, and cholinesterase inhibitors.

[21] The method according to any of [13] to [19], wherein the aqueous composition further contains one or more selected from the group consisting of nipradilol, dorzolamide, brinzolamide, timolol, a salt of nipradilol, a salt of dorzolamide, a salt of brinzolamide, a salt of timolol, a solvate of nipradilol or the salt thereof, a solvate of dorzolamide or the salt thereof, a solvate of brinzolamide or the salt thereof, and a solvate of timolol or the salt thereof.

[0023]

[22] The method according to any of [13] to [21], further comprising the step of housing the aqueous composition in a container made of polyolefin-based resin.

[23] The method according to [22], wherein the polyolefin-based resin is polyethylene or polypropylene.

[24] The method according to [22] or [23], wherein the container made of polyolefin-based resin is a container for eye drops.

[0024]

[25] A method for suppressing crystal precipitation of an aqueous composition, the method comprising the step of incorporating a prostaglandin in an aqueous composition comprising a compound represented by Formula (1) or a salt thereof, or a solvate of the compound or the salt thereof.

[26] The method according to [25], wherein the compound represented by Formula (1) is ripasudil.

[27] The method according to [25] or [26], wherein the prostaglandin is one or more selected from the group consisting of isopropyl unoprostone, tafluprost, travoprost, bimatoprost, latanoprost, a salt of isopropyl unoprostone, a salt of tafluprost, a salt of travoprost, a salt of bimatoprost, a salt of latanoprost, a solvate of isopropyl unoprostone or the salt thereof, a solvate of tafluprost or the salt thereof, a solvate of travoprost or the salt thereof, a solvate of bimatoprost or the salt thereof, and a solvate of latanoprost or the salt thereof.

[28] The method according to [25] or [26], wherein the prostaglandin is one or more selected from the group consisting of tafluprost, travoprost, bimatoprost, latanoprost, a salt of tafluprost, a salt of travoprost, a salt of bimatoprost, a salt of latanoprost, a solvate of tafluprost or the salt thereof, a solvate of travoprost or the salt thereof, a solvate of bimatoprost or the salt thereof, and a solvate of latanoprost or the salt thereof.

[29] The method according to any of [25] to [28], wherein the aqueous composition is an ophthalmic agent.

[30] The method according to [29], wherein the ophthalmic agent is an eye drop.

[31] The method according to any of [25] to [30], wherein the aqueous composition is a prophylactic and/or therapeutic agent for a disease selected from the group

consisting of ocular hypertension, glaucoma, and ocular fundus diseases.

[0025]

[32] The method according to any of [25] to [31], wherein the aqueous composition further contains one or more selected from the group consisting of $\alpha 1$ receptor blockers, $\alpha 2$ receptor agonists, β blockers, carbonic anhydrase inhibitors, sympathomimetics, parasympathomimetics, calcium antagonists, and cholinesterase inhibitors.

[33] The method according to any of [25] to [31], wherein the aqueous composition further contains one or more selected from the group consisting of nipradilol, dorzolamide, brinzolamide, timolol, a salt of nipradilol, a salt of dorzolamide, a salt of brinzolamide, a salt of timolol, a solvate of nipradilol or the salt thereof, a solvate of dorzolamide or the salt thereof, a solvate of brinzolamide or the salt thereof, and a solvate of timolol or the salt thereof.

[0026]

Examples of the halogen atom in Formula (1) include a fluorine atom, a chlorine atom, and a bromine atom. In Formula (1), a fluorine atom or a bromine atom is preferred as the halogen atom, and a fluorine atom is particularly preferred.

Further, in Formula (1), the carbon atom forming the homopiperazine ring substituted with the methyl group is an asymmetric carbon atom. As a result, stereoisomerism

occurs. The compound represented by Formula (1) includes all the stereoisomers, and may be a single stereoisomer or a mixture of various stereoisomers at any given ratio. Preferred as the compound represented by Formula (1) is a compound having the S configuration as the absolute configuration.

[0027]

The salt of the compound represented by Formula (1) is not particularly limited as long as it is a pharmacologically acceptable salt, and specific examples of the salt include inorganic acid salts such as hydrochloride, sulfate, nitrate, hydrofluoride, and hydrobromate; and organic acid salts such as acetate, tartrate, lactate, citrate, fumarate, maleate, succinate, methanesulfonate, ethanesulfonate, benzenesulfonate, toluenesulfonate, naphthalenesulfonate, and camphorsulfonate, with hydrochloride being preferred.

The compound represented by Formula (1) or a salt thereof may also be in the form of a hydrate or a solvate such as an alcohol solvate, and is preferably in the form of a hydrate.

[0028]

Specific examples of the compound represented by Formula (1) or a salt thereof or a solvate of the compound or the salt thereof include:

ripasudil (chemical name: 4-fluoro-5-{[(2S)-2-methyl-1,4-diazepan-1-yl]sulfonyl}isoquinoline) or a salt

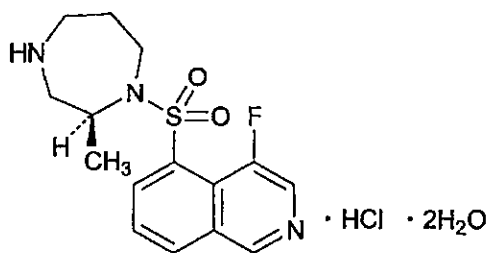
thereof or a solvate of ripasudil or the salt thereof;
and

4-bromo-5-{[(2S)-2-methyl-1,4-diazepan-1-yl]sulfonyl}isoquinoline or a salt thereof or a solvate of 4-bromo-5-{[(2S)-2-methyl-1,4-diazepan-1-yl]sulfonyl}isoquinoline or the salt thereof.

[0029]

The compound represented by Formula (1) or a salt thereof or a solvate thereof is preferably ripasudil or a salt thereof or a solvate of ripasudil or the salt thereof, or 4-bromo-5-{[(2S)-2-methyl-1,4-diazepan-1-yl]sulfonyl}isoquinoline or a salt thereof or a solvate of 4-bromo-5-{[(2S)-2-methyl-1,4-diazepan-1-yl]sulfonyl}isoquinoline or the salt thereof, more preferably ripasudil or a salt thereof or a solvate of ripasudil or the salt thereof, still more preferably ripasudil or a hydrochloride thereof or a hydrate of ripasudil or the hydrochloride thereof, and particularly preferably a ripasudil hydrochloride hydrate (ripasudil monohydrochloride dihydrate) represented by the following structural formula:

[0030]



[0031]

[0032]

The compound represented by Formula (1) or a salt thereof or a solvate of the compound or the salt thereof is known and can be produced using a known method. Specifically, ripasudil or a salt thereof or a solvate of ripasudil or the salt thereof can be produced using the method described in WO1999/020620 or WO2006/057397, for example. 4-Bromo-5-{[(2S)-2-methyl-1,4-diazepan-1-yl]sulfonyl}isoquinoline or a salt thereof or a solvate of 4-bromo-5-{[(2S)-2-methyl-1,4-diazepan-1-yl]sulfonyl}isoquinoline or the salt thereof can be produced using the method described in WO2006/115244, for example.

[0033]

The content of the compound represented by Formula (1) or a salt thereof or a solvate of the compound or the salt thereof in the aqueous composition is not particularly limited, and may be determined as appropriate, in consideration of the target disease, or the sex, age, or symptoms of the patient, for example. From the viewpoint of achieving excellent pharmacological action, however, the content of the compound represented by Formula (1) or a salt thereof or a solvate of the compound or the salt thereof is preferably 0.01 to 10 w/v%, more preferably 0.02 to 8 w/v%, and particularly preferably 0.04 to 6 w/v%, calculated as the free form of the compound represented by Formula (1), based on the

total volume of the aqueous composition. In particular, when ripasudil is used as the compound represented by Formula (1), from the viewpoint of achieving excellent pharmacological action, the content of ripasudil or a salt thereof or a solvate of ripasudil or the salt thereof is preferably 0.05 to 5 w/v%, more preferably 0.1 to 3 w/v%, and particularly preferably 0.15 to 2 w/v%, calculated as the free form, based on the total volume of the aqueous composition.

[0034]

As used herein, the "prostaglandin" means a prostaglandin or a derivative thereof, and specific examples of such prostaglandins include isopropyl unoprostone (chemical name: (+)-isopropyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-(3-oxodecyl)cyclopentyl]hept-5-enoate), tafluprost (chemical name: 1-methylethyl (5Z)-7-[(1R,2R,3R,5S)-2-[(1E)-3,3-difluoro-4-phenoxy-1-butenyl]-3,5-dihydroxycyclopentyl]-5-heptenoate), travoprost (chemical name: isopropyl (5Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(1E,3R)-3-hydroxy-4-[3-(trifluoromethyl)phenoxy]but-1-enyl]cyclopentyl]hept-5-enoate), bimatoprost (chemical name: (5Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(1E,3S)-3-hydroxy-5-phenylpent-1-en-1-yl]cyclopentyl]-N-ethylhept-5-enamide), latanoprost (chemical name: (+)-isopropyl (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(3R)-3-hydroxy-5-phenylpentyl]cyclopentyl]-5-heptenoate), pharmaceutically acceptable salts thereof, and solvates of such a compound

or pharmaceutically acceptable salt thereof with water, an alcohol, or the like, and these can be used singly or in combination of two or more.

Preferred as the prostaglandin is one or more selected from the group consisting of tafluprost, travoprost, bimatoprost, latanoprost, a salt of tafluprost, a salt of travoprost, a salt of bimatoprost, a salt of latanoprost, a solvate of tafluprost or the salt thereof, a solvate of travoprost or the salt thereof, a solvate of bimatoprost or the salt thereof, and a solvate of latanoprost or the salt thereof.

Each of these prostaglandins is known, and may be produced using a known method, or a commercially available product may be used.

[0035]

The prostaglandin has reducing action for discoloration during high-temperature preservation, and in addition suppressing action for crystal precipitation during low-temperature preservation. As specifically disclosed in Test Example 2, it was found that, although the aqueous composition containing the compound represented by Formula (1) typified by ripasudil or a salt thereof or a solvate of the compound or the salt thereof can suffer from crystal precipitation during low-temperature preservation, further incorporation of latanoprost in the aqueous composition suppresses crystal precipitation during low-temperature preservation in comparison with the case where the aqueous composition

does not contain latanoprost. Accordingly, the aqueous composition containing the compound represented by Formula (1) or a salt thereof or a solvate of the compound or the salt thereof and the prostaglandin undergoes reduced discoloration during high-temperature preservation, and in addition is suppressed from crystal precipitation during low-temperature preservation, and thus has an advantage of excellent preservation stability.

[0036]

While the content of the prostaglandin in the aqueous composition is not particularly limited, from the viewpoint of discoloration-reducing action and/or crystal precipitation-suppressing action, the content of the prostaglandin is preferably 0.00005 to 1.0 w/v%, more preferably 0.00025 to 0.25 w/v%, and particularly preferably 0.00075 to 0.075 w/v% based on the total volume of the aqueous composition.

While the content ratio by mass of the prostaglandin to the compound represented by Formula (1) or a salt thereof or a solvate of the compound or the salt thereof in the aqueous composition is not particularly limited, from the viewpoint of discoloration-reducing action and/or crystal precipitation-suppressing action, the content ratio by mass of the prostaglandin is preferably 0.0001 to 4 parts by mass, more preferably 0.00125 to 1.25 parts by mass, and particularly preferably 0.005 to 0.5 parts by mass, with respect to 1 part by mass of the compound represented by Formula (1) calculated as the

free form. In particular, when the compound represented by Formula (1) or a salt thereof or a solvate of the compound or the salt thereof is ripasudil or a salt thereof or a solvate of ripasudil or the salt thereof, from the viewpoint of discoloration-reducing action and/or crystal precipitation-suppressing action, the content ratio by mass of the prostaglandin is preferably 0.0005 to 2 parts by mass, more preferably 0.0025 to 0.75 parts by mass, and particularly preferably 0.0075 to 0.25 parts by mass, with respect to 1 part by mass of ripasudil or a salt thereof or a solvate of ripasudil or the salt thereof calculated as the free form.

[0037]

In particular, when the prostaglandin is tafluprost or a salt thereof or a solvate of tafluprost or the salt thereof, from the viewpoint of discoloration-reducing action and/or crystal precipitation-suppressing action, the content of tafluprost or a salt thereof or a solvate of tafluprost or the salt thereof is preferably 0.0001 to 0.02 w/v%, more preferably 0.0005 to 0.01 w/v%, and particularly preferably 0.001 to 0.005 w/v%, calculated as the free form of tafluprost, based on the total volume of the aqueous composition.

While the content ratio by mass of tafluprost or a salt thereof or a solvate of tafluprost or the salt thereof to the compound represented by Formula (1) or a salt thereof or a solvate of the compound or the salt thereof in the aqueous composition is not particularly

limited, from the viewpoint of discoloration-reducing action and/or crystal precipitation-suppressing action, the content ratio by mass of tafluprost or a salt thereof or a solvate of tafluprost or the salt thereof is preferably 0.0001 to 0.025 parts by mass, more preferably 0.0007 to 0.015 parts by mass, and particularly preferably 0.002 to 0.005 parts by mass, calculated as the free form, with respect to 1 part by mass of the compound represented by Formula (1) calculated as the free form. In particular, when the compound represented by Formula (1) or a salt thereof or a solvate of the compound or the salt thereof is ripasudil or a salt thereof or a solvate of ripasudil or the salt thereof, from the viewpoint of discoloration-reducing action and/or crystal precipitation-suppressing action, the content ratio by mass of tafluprost or a salt thereof or a solvate of tafluprost or the salt thereof is preferably 0.0005 to 0.02 parts by mass, more preferably 0.001 to 0.01 parts by mass, and particularly preferably 0.003 to 0.004 parts by mass, calculated as the free form, with respect to 1 part by mass of ripasudil or a salt thereof or a solvate of ripasudil or the salt thereof calculated as the free form.

[0038]

When the prostaglandin is travoprost or a salt thereof or a solvate of travoprost or the salt thereof, from the viewpoint of discoloration-reducing action and/or crystal precipitation-suppressing action, the

content of travoprost or a salt thereof or a solvate of travoprost or the salt thereof is preferably 0.0001 to 0.05 w/v%, more preferably 0.0005 to 0.01 w/v%, and particularly preferably 0.001 to 0.005 w/v%, calculated as the free form of travoprost, based on the total volume of the aqueous solution.

While the content ratio by mass of travoprost or a salt thereof or a solvate of travoprost or the salt thereof to the compound represented by Formula (1) or a salt thereof or a solvate of the compound or the salt thereof in the aqueous composition is not particularly limited, from the viewpoint of discoloration-reducing action and/or crystal precipitation-suppressing action, the content ratio by mass of travoprost or a salt thereof or a solvate of travoprost or the salt thereof is preferably 0.00025 to 0.03 parts by mass, more preferably 0.00075 to 0.07 parts by mass, and particularly preferably 0.0025 to 0.03 parts by mass, calculated as the free form, with respect to 1 part by mass of the compound represented by Formula (1) calculated as the free form. In particular, when the compound represented by Formula (1) or a salt thereof or a solvate thereof is ripasudil or a salt thereof or a solvate of the compound or the salt thereof, from the viewpoint of discoloration-reducing action and/or crystal precipitation-suppressing action, the content ratio by mass of travoprost or a salt thereof or a solvate of travoprost or the salt thereof is preferably 0.0005 to 0.1 parts by mass, more preferably

0.001 to 0.05 parts by mass, and particularly preferably 0.005 to 0.02 parts by mass, calculated as the free form, with respect to 1 part by mass of ripasudil or a salt thereof or a solvate of ripasudil or the salt thereof calculated as the free form.

[0039]

When the prostaglandin is bimatoprost or a salt thereof or a solvate of bimatoprost or the salt thereof, from the viewpoint of discoloration-reducing action and/or crystal precipitation-suppressing action, the content of bimatoprost or a salt thereof or a solvate of bimatoprost or the salt thereof is preferably 0.001 to 0.5 w/v%, more preferably 0.005 to 0.1 w/v%, and particularly preferably 0.01 to 0.05 w/v%, calculated as the free form of bimatoprost, based on the total volume of the aqueous composition.

While the content ratio by mass of bimatoprost or a salt thereof or a solvate of bimatoprost or the salt thereof to the compound represented by Formula (1) or a salt thereof or a solvate of the compound or the salt thereof in the aqueous composition is not particularly limited, from the viewpoint of discoloration-reducing action and/or crystal precipitation-suppressing action, the content ratio by mass of bimatoprost or a salt thereof or a solvate of bimatoprost or the salt thereof is preferably 0.001 to 2 parts by mass, more preferably 0.0075 to 0.75 parts by mass, and particularly preferably 0.025 to 0.3 parts by mass, calculated as the free form,

with respect to 1 part by mass of the compound represented by Formula (1) calculated as the free form. In particular, when the compound represented by Formula (1) or a salt thereof or a solvate of the compound or the salt thereof is ripasudil or a salt thereof or a solvate of ripasudil or the salt thereof, from the viewpoint of discoloration-reducing action and/or crystal precipitation-suppressing action, the content ratio by mass of bimatoprost or a salt thereof or a solvate of bimatoprost or the salt thereof is preferably 0.005 to 1 parts by mass, more preferably 0.01 to 0.5 parts by mass, and particularly preferably 0.05 to 0.1 parts by mass, calculated as the free form, with respect to 1 part by mass of ripasudil or a salt thereof or a solvate of ripasudil or the salt thereof calculated as the free form.

[0040]

Further, when the prostaglandin is latanoprost or a salt thereof or a solvate of latanoprost or the salt thereof, from the viewpoint of discoloration-reducing action and/or crystal precipitation-suppressing action, the content of latanoprost or a salt thereof or a solvate of latanoprost or the salt thereof is preferably 0.0001 to 0.1 w/v%, more preferably 0.0005 to 0.05 w/v%, and particularly preferably 0.001 to 0.01 w/v%, calculated as the free form, based on the total volume of the aqueous composition.

While the content ratio by mass of latanoprost or a salt thereof or a solvate of latanoprost or the salt

thereof to the compound represented by Formula (1) or a salt thereof or a solvate of the compound or the salt thereof in the aqueous composition is not particularly limited, from the viewpoint of discoloration-reducing action and/or crystal precipitation-suppressing action, the content ratio by mass of latanoprost or a salt thereof or a solvate of latanoprost or the salt thereof is preferably 0.0005 to 0.1 parts by mass, more preferably 0.0025 to 0.04 parts by mass, and particularly preferably 0.0075 to 0.03 parts by mass, calculated as the free form, with respect to 1 part by mass of the compound represented by Formula (1) calculated as the free form. In particular, when the compound represented by Formula (1) or a salt thereof or a solvate of the compound or the salt thereof is ripasudil or a salt thereof or a solvate of ripasudil or the salt thereof, from the viewpoint of discoloration-reducing action and/or crystal precipitation-suppressing action, the content ratio by mass of latanoprost or a salt thereof or a solvate of latanoprost or the salt thereof is preferably 0.001 to 0.05 parts by mass, more preferably 0.005 to 0.02 parts by mass, and particularly preferably 0.01 to 0.015 parts by mass, calculated as the free form, with respect to 1 part by mass of ripasudil or a salt thereof or a solvate of ripasudil or the salt thereof calculated as the free form.

[0041]

As used herein, the "aqueous composition" means a composition containing at least water, which may be in the form of a liquid (solution or suspension) or a semi-solid (ointment), for example, and preferably in the form of a liquid. As the water in the composition, purified water, water for injection, or sterile purified water, for example, can be used.

While the content of water in the aqueous composition is not particularly limited, it is preferably 5 mass% or more, more preferably 20 mass% or more, still more preferably 50 mass% or more, even more preferably 90 mass% or more, and particularly preferably 90 to 99.8 mass%.

[0042]

The aqueous composition can be prepared into various dosage forms in accordance with known methods described in the General Rules for Preparations in the Japanese Pharmacopoeia 16th Edition, for example. Examples of dosage forms include injections, inhalation solutions, eye drops, eye ointments, ear drops, nasal drops, enemas, liquids for external use, sprays, ointments, gels, oral liquids, and syrups. From the viewpoint of advantageously utilizing the pharmacological action of the compound represented by Formula (1), the dosage form is an ophthalmic agent, which specifically is preferably an eye drop or an eye ointment, and is particularly preferably an eye drop.

[0043]

The aqueous composition may contain, in addition to the components described above, additives used in drugs, quasi drugs, and the like, in accordance with the dosage form. Examples of such additives include inorganic salts, isotonic agents, chelating agents, stabilizers, pH regulators, antiseptics, antioxidants, thickeners, surfactants, solubilizers, suspending agents, cooling agents, dispersants, preservatives, oily bases, emulsion bases, and water-soluble bases.

Specific examples of these additives include ascorbic acid, potassium aspartate, sodium bisulfite, alginic acid, sodium benzoate, benzyl benzoate, epsilon-aminocaproic acid, fennel oil, ethanol, ethylene-vinyl acetate copolymer, sodium edetate, tetrasodium edetate, potassium chloride, calcium chloride hydrate, sodium chloride, magnesium chloride, hydrochloric acid, alkyl diaminoethylglycine hydrochloride solution, carboxyvinyl polymer, dried sodium sulfite, dried sodium carbonate, d-camphor, dl-camphor, xylitol, citric acid hydrate, sodium citrate hydrate, glycerin, gluconic acid, L-glutamic acid, monosodium L-glutamate, creatinine, chlorhexidine gluconate solution, chlorobutanol, sodium dihydrogenphosphate dihydrate, geraniol, sodium chondroitin sulfate, acetic acid, potassium acetate, sodium acetate hydrate, titanium oxide, gellan gum, dibutylhydroxytoluene, potassium bromide, benzododecinium bromide, tartaric acid, sodium hydroxide, polyoxyl 45 stearate, purified lanolin, D-sorbitol, sorbitol solution,

taurine, sodium bicarbonate, sodium carbonate hydrate, sodium thiosulfate hydrate, thimerosal, tyloxapol, sodium dehydroacetate, trometamol, concentrated glycerin, mixed tocopherol concentrate, white petrolatum, mentha water, mentha oil, benzalkonium chloride concentrated solution 50, ethyl parahydroxybenzoate, butyl parahydroxybenzoate, propyl parahydroxybenzoate, methyl parahydroxybenzoate, sodium hyaluronate, human serum albumin, hydroxyethyl cellulose, hydroxypropyl cellulose, hypromellose, glacial acetic acid, sodium pyrosulfite, phenylethyl alcohol, glucose, propylene glycol, bergamot oil, benzalkonium chloride, benzalkonium chloride solution, benzyl alcohol, benzethonium chloride, benzethonium chloride solution, borax, boric acid, povidone, polyoxyethylene (200) polyoxypropylene glycol (70), sodium polystyrene sulfonate, polysorbate 80, polyoxyethylene hydrogenated castor oil 60, partially hydrolyzed polyvinyl alcohol, d-borneol, macrogol 4000, macrogol 6000, D-mannitol, anhydrous citric acid, anhydrous sodium monohydrogen phosphate, anhydrous sodium dihydrogen phosphate, methanesulfonic acid, methylcellulose, l-menthol, monoethanolamine, aluminum monostearate, polyethylene glycol monostearate, eucalyptus oil, potassium iodide, sulfuric acid, oxyquinoline sulfate, liquid paraffin, borneo camphor, phosphoric acid, dibasic sodium phosphate hydrate, potassium dihydrogenphosphate, sodium dihydrogenphosphate, sodium dihydrogenphosphate monohydrate, malic acid, and petrolatum.

[0044]

Examples of preferred additives include potassium chloride, calcium chloride hydrate, sodium chloride, magnesium chloride, glycerin, acetic acid, potassium acetate, sodium acetate hydrate, tartaric acid, sodium hydroxide, sodium bicarbonate, sodium carbonate hydrate, concentrated glycerin, hydroxyethyl cellulose, hydroxypropyl cellulose, hypromellose, borax, boric acid, povidone, polysorbate 80, polyoxyethylene hydrogenated castor oil, polyethylene glycol monostearate, partially hydrolyzed polyvinyl alcohol, macrogol 4000, macrogol 6000, anhydrous citric acid, anhydrous sodium monohydrogen phosphate, anhydrous sodium dihydrogen phosphate, methylcellulose, monoethanolamine, phosphoric acid, dibasic sodium phosphate hydrate, potassium dihydrogenphosphate, sodium dihydrogenphosphate, sodium dihydrogenphosphate monohydrate, sodium hyaluronate, glucose, and l-menthol.

[0045]

The aqueous composition may further contain, in addition to the components described above, other medicinal components in accordance with the target disease and the like. Examples of such medicinal components include $\alpha 1$ receptor blockers including bunazosin or a salt thereof or a solvate of bunazosin or the salt thereof, such as bunazosin hydrochloride; $\alpha 2$ receptor agonists including brimonidine or a salt thereof or a solvate of brimonidine or the salt thereof, such as

brimonidine tartrate, and apraclonidine or a salt thereof or a solvate of apraclonidine or the salt thereof; β blockers including carteolol or a salt thereof or a solvate of carteolol or the salt thereof, such as carteolol hydrochloride, nipradilol or a salt thereof or a solvate of nipradilol or the salt thereof, timolol or a salt thereof or a solvate of timolol or the salt thereof, such as timolol maleate, betaxolol or a salt thereof or a solvate of betaxolol or the salt thereof, such as betaxolol hydrochloride, levobunolol or a salt thereof or a solvate of levobunolol or the salt thereof, such as levobunolol hydrochloride, befunolol or a salt thereof or a solvate of befunolol or the salt thereof, and metipranolol or a salt thereof or a solvate of metipranolol or the salt thereof; carbonic anhydrase inhibitors including dorzolamide or a salt thereof or a solvate of dorzolamide or the salt thereof, such as dorzolamide hydrochloride, brinzolamide or a salt thereof or a solvate of brinzolamide or the salt thereof, acetazolamide or a salt thereof or a solvate of acetazolamide or the salt thereof, dichlorphenamide or a salt thereof or a solvate of dichlorphenamide or the salt thereof, and methazolamide or a salt thereof or a solvate of methazolamide or the salt thereof; sympathomimetics including dipivefrine or a salt thereof or a solvate of dipivefrine or the salt thereof, such as dipivefrine hydrochloride, and epinephrine or a salt thereof or a solvate of epinephrine or the salt thereof, such as

epinephrine, epinephrine borate, or epinephrine hydrochloride; parasympathomimetics including distigmine bromide or a salt thereof or a solvate of distigmine bromide or the salt thereof, pilocarpine or a salt thereof or a solvate of pilocarpine or the salt thereof, such as pilocarpine, pilocarpine hydrochloride, or pilocarpine nitrate, and carbachol or a salt thereof or a solvate of carbachol or the salt thereof; calcium antagonists including lomerizine or a salt thereof or a solvate of lomerizine or the salt thereof, such as lomerizine hydrochloride; and cholinesterase inhibitors including demecarium or a salt thereof or a solvate of demecarium or the salt thereof, echothiophate or a salt thereof or a solvate of echothiophate or the salt thereof, and physostigmine or a salt thereof or a solvate of physostigmine or the salt thereof. One or more of these medicinal components can be incorporated.

Preferred as the other medicinal components is one or more selected from the group consisting of nipradilol, dorzolamide, brinzolamide, timolol, a salt of nipradilol, a salt of dorzolamide, a salt of brinzolamide, a salt of timolol, a solvate of nipradilol or the salt thereof, a solvate of dorzolamide or the salt thereof, a solvate of brinzolamide or the salt thereof, and a solvate of timolol or the salt thereof.

[0046]

The pH of the aqueous composition is not particularly limited, but is preferably 4 to 9, more

preferably 4.5 to 8, and particularly preferably 5 to 7. The osmotic pressure ratio of the aqueous composition relative to physiological saline is not particularly limited, but is preferably 0.6 to 3, and particularly preferably 0.6 to 2.

[0047]

The aqueous composition is preferably stored in a container, from the viewpoint of preservation stability and portability, and the like. As used herein, the "container" means a package for directly storing the aqueous composition. The container is a concept that includes all of the "well-closed container", "tight container", and "hermetic container" defined in the General Notices in the Japanese Pharmacopoeia 16th Edition.

[0048]

The form of the container is not particularly limited as long as it can store an aqueous composition, and may be selected or set as appropriate, depending on the dosage form, for example. Specific examples of such forms of the container include containers for injections, containers for inhalations, containers for sprays, bottle-shaped containers, tubular containers, containers for eye drops, containers for nasal drops, containers for ear drops, and bag containers. The container may be further packaged in a box, a bag, or the like.

[0049]

The material of the container is not particularly limited, and may be selected as appropriate depending on the form of the container. Specific examples of materials include glass, plastics, cellulose, pulp, rubber, and metals, and preferably a plastic from the viewpoint of processability, squeezability, and durability. The resin for a container made of a plastic is preferably a thermoplastic resin. Examples of such resins include polyolefin-based resins such as low-density polyethylene (including linear low-density polyethylene), high-density polyethylene, medium-density polyethylene, polypropylene, and cyclic polyolefins; polyester-based resins such as polyethylene terephthalate, polybutylene terephthalate, polyethylene naphthalate, polybutylene naphthalate, and poly(1,4-cyclohexylene dimethylene terephthalate); polyphenylene ether-based resins; polycarbonate-based resins; polysulfone-based resins; polyamide-based resins; polyvinyl chloride resins; and styrene-based resins. A mixture of these resins (polymer alloy) may also be used.

While the material of the container is not particularly limited, from the viewpoint of discoloration-reducing action, it is preferably a polyolefin-based resin, and particularly preferably polypropylene. As described in Test Examples below, discoloration is particularly prominently reduced in the case of a container made of polyolefin-based resin.

[0050]

As used herein, the "container made of polyolefin-based resin" means a container in which at least a portion that contacts the aqueous composition is "made of polyolefin-based resin". Accordingly, a container in which, for example, a polyolefin layer is provided as the inner layer that contacts the aqueous composition and a different resin material or the like is, for example, laminated on the outer side of the inner layer also corresponds to the "container made of polyolefin-based resin". The polyolefin-based resin is not particularly limited herein, and may be a polymer of a single monomer (homopolymer) or a copolymer of a plurality of monomers (copolymer). In the case of a copolymer, the mode of polymerization is not particularly limited, and may be random polymerization or block polymerization. Further, the stereoregularity (tacticity) of the polyolefin-based resin is not particularly limited.

Specific examples of such polyolefin-based resins include polyethylene (more specifically, such as low-density polyethylene (including linear low density polyethylene), high-density polyethylene, and medium-density polyethylene), polypropylene, cyclic polyolefins, poly(4-methylpentene), polytetrafluoroethylene, ethylene-propylene copolymer, ethylene- α -olefin copolymer, ethylene-acrylic acid copolymer, ethylene-methacrylic acid copolymer, ethylene-vinylacetate copolymer, and ethylene-ethyl acrylate copolymer. These polyolefin-based resins can be used singly or in combination of two

or more. As the polyolefin-based resin, polyethylene, polypropylene, or a cyclic polyolefin is preferred, and polyethylene or polypropylene is more preferred, and polypropylene is particularly preferred, from the viewpoint of reducing the discoloration.

As used herein, the expression "made of polyolefin-based resin" means that the polyolefin-based resin is included in at least a portion of the material, and "made of polyolefin-based resin" also includes, for example, a mixture of two or more resins (polymer alloy), which are a polyolefin-based resin and other resins.

[0051]

A substance that prevents transmission of ultraviolet light, such as an ultraviolet absorber or an ultraviolet scattering agent, is preferably further mixed into the container made of polyolefin-based resin. This improves photostability of the compound represented by Formula (1). Specific examples of such substances, for example, specific examples of ultraviolet scattering agents include titanium oxide and zinc oxide. Examples of ultraviolet absorbers include benzotriazole-based ultraviolet absorbers such as 2-(2H-benzotriazol-2-yl)-p-cresol (for example, Tinuvin P: BASF Corporation), 2-(2H-benzotriazol-2-yl)-4,6-bis(1-methyl-1-phenylethyl)phenol (for example, Tinuvin 234: BASF Corporation), 2-(3,5-di-*t*-butyl-2-hydroxyphenyl)benzotriazole (for example, Tinuvin 320: BASF Corporation), 2-[5-chloro(2H)-benzotriazol-2-yl]-4-methyl-6-(*tert*-butyl)phenol (for

example, Tinuvin 326: BASF Corporation), 2-(3,5-di-tert-butyl-2-hydroxyphenyl)-5-chlorobenzotriazole (for example, Tinuvin 327: BASF Corporation), 2-(2H-benzotriazol-2-yl)-4,6-di-tert-pentylphenol (for example, Tinuvin PA328: BASF Corporation), 2-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol (for example, Tinuvin 329: BASF Corporation), 2,2'-methylenebis[6-(2H-benzotriazol-2-yl)-4-(1,1,3,3-tetramethylbutyl)phenol (for example, Tinuvin 360: BASF Corporation), a reaction product of methyl 3-(3-(2H-benzotriazol-2-yl)-5-tert-butyl-4-hydroxyphenyl)propionate and polyethylene glycol 300 (for example, Tinuvin 213: BASF Corporation), 2-(2H-benzotriazol-2-yl)-6-dodecyl-4-methylphenol (for example, Tinuvin 571: BASF Corporation), 2-(2'-hydroxy-3',5'-di-tert-amylphenyl)benzotriazole, 2-[2'-hydroxy-3'-(3'',4'',5'',6''-tetrahydrophthalimidomethyl)-5'-methylphenyl]benzotriazole, and 2,2'-methylenebis[4-(1,1,3,3-tetramethylbutyl)-6-(2H-benzotriazol-2-yl)phenol];

cyanoacrylate-based ultraviolet absorbers such as 2,2-bis{[2-cyano-3,3-diphenylacryloyloxy]methyl}propane-1,3-diyl=bis(2-cyano-3,3-diphenylacrylate) (for example, Uvinul 3030 FF: BASF Corporation), ethyl 2-cyano-3,3-diphenylacrylate (for example, Uvinul 3035: BASF Corporation), and 2-ethylhexyl 2-cyano-3,3-diphenylacrylate (for example, Uvinul 3039: BASF Corporation); triazine-based ultraviolet absorbers such as 2-(4,6-diphenyl-1,3,5-triazin-2-yl)-5-[(hexyl)oxy]-

phenol (for example, Tinuvin 1577 ED: BASF Corporation); benzophenone-based ultraviolet absorbers such as octabenzene (for example, Chimassorb 81: BASF Corporation), 2,2'-dihydroxy-4,4'-dimethoxybenzophenone (for example, Uvinul 3049: BASF Corporation), 2,2'-4,4'-tetrahydrobenzophenone (for example, Uvinul 3050: BASF Corporation), oxybenzone, hydroxymethoxybenzophenonesulfonic acid, sodium hydroxymethoxybenzophenone sulfonate, dihydroxydimethoxybenzophenone, sodium dihydroxydimethoxybenzophenone disulfonate, dihydroxybenzophenone, and tetrahydroxybenzophenone; cinnamate-based ultraviolet absorbers such as methyl diisopropylcinnamate, cinoxate, glyceryl mono-2-ethylhexanoate di-p-methoxycinnamate, isopropyl p-methoxycinnamate-diisopropyl cinnamate ester mixture, 2-ethylhexyl p-methoxycinnamate, and benzyl cinnamate; benzoate-based ultraviolet absorbers such as p-aminobenzoic acid, ethyl p-aminobenzoate, glyceryl p-aminobenzoate, amyl p-dimethylaminobenzoate, 2-ethylhexyl p-dimethylaminobenzoate, and ethyl 4-[N,N-di(2-hydroxypropyl)amino]benzoate; salicylate-based ultraviolet absorbers such as ethylene glycol salicylate, octyl salicylate, dipropylene glycol salicylate, phenyl salicylate, homomenthyl salicylate, and methyl salicylate; guaiazulene; 2-ethylhexyl dimethoxybenzylidene dioxoimidazolidine propionate; 2,4,6-tris[4-(2-ethylhexyloxycarbonyl)anilino]1,3,5-

triazine; p-hydroxyanisole; 4-tert-butyl-4'-methoxydibenzoylmethane; phenylbenzimidazole sulfonate; and hexyl 2-(4-diethylamino-2-hydroxybenzoyl)benzoate.

[0052]

When a substance that prevents transmission of ultraviolet light is mixed into the container, the proportion of the substance to be incorporated varies depending on the type of the substance and the like, but it may be 0.001 to 50 mass%, for example, preferably 0.002 to 25 mass%, and particularly preferably about 0.01 to 10 mass%, in the container.

[0053]

The inside of the container is preferably visible (observable) by the naked eye. When the inside is visible, the following advantages are produced. For example, the presence or absence of any foreign matter can be inspected in the manufacturing steps of the pharmaceutical preparation, and the residual amount of the contents (aqueous composition) can be examined by a user of the pharmaceutical preparation. The visibility may be ensured in at least a portion of the surface of the container (for example, even if the side surface of a container for eye drops cannot be seen through due to the presence of a shrinkable film or the like, it can be determined as visible if the bottom surface of the container is visible.). If the inside is visible through a portion of the surface of the container, then the aqueous composition in the container is visible.

[0054]

The means for storing the aqueous composition into the container is not particularly limited, and the container may be filled with the aqueous composition using a conventional method, in accordance with the form of the container and the like.

[0055]

The disease targeted by the aqueous composition or the pharmaceutical preparation is not particularly limited, and may be selected as appropriate depending on the pharmacological action or the like of the compound represented by Formula (1).

Specifically, the aqueous composition or pharmaceutical preparation can be used, for example, as a prophylactic or therapeutic agent for ocular hypertension or glaucoma, based on the Rho kinase inhibitory action or intraocular pressure-lowering action of the compound represented by Formula (1), and the intraocular pressure-lowering action of the prostaglandin. This is preferred because the intraocular pressure-lowering action of the compound represented by Formula (1) and the intraocular pressure-lowering action of the prostaglandin are combined to produce excellent intraocular pressure-lowering action, which leads to achievement of excellent prophylactic and/or therapeutic action for ocular hypertension or glaucoma. More specifically, examples of types of glaucoma include primary open-angle glaucoma, normal-tension glaucoma, hypersecretion glaucoma, acute

closed-angle glaucoma, chronic closed-angle glaucoma, plateau iris syndrome, combined mechanism glaucoma, steroid-induced glaucoma, capsular glaucoma, pigmentary glaucoma, amyloid-associated glaucoma, neovascular glaucoma, and malignant glaucoma.

[0056]

Further, as disclosed in JP-B-5557408, the pharmaceutical preparation may be used as a prophylactic or therapeutic agent for ocular fundus diseases (lesions that mainly develop in the retina and/or choroidea; specifically, for example, hypertensive or arteriosclerotic ocular fundus abnormalities, central retinal artery occlusion, retinal vein occlusion such as central retinal vein occlusion or branch retinal vein occlusion, diabetic retinopathy, diabetic macular edema, diabetic maculopathy, Eales disease, congenital retinal vascular abnormalities such as Coats disease, von Hippel disease, pulseless disease, macular diseases (such as central serous chorioretinopathy, cystoid macular edema, age-related macular degeneration, macular hole, myopic macular degeneration, vitreoretinal interface maculopathy, drug-related maculopathy, or heredomacular degeneration), retinal detachment such as rhegmatogenous, tractional, exudative, or the like, retinitis pigmentosa, or retinopathy of prematurity) based on the action of the compound represented by Formula (1). More preferably, the pharmaceutical preparation may be used as a prophylactic or therapeutic agent for diabetic

retinopathy, diabetic macular edema, or age-related macular degeneration.

[0057]

When the aqueous composition or pharmaceutical preparation is used as a prophylactic and/or therapeutic agent for an eye disease (preferably, a disease selected from the group consisting of ocular hypertension, glaucoma, and ocular fundus diseases, particularly preferably a disease selected from the group consisting of ocular hypertension and glaucoma), the aqueous composition or pharmaceutical preparation may be administered about one to three times per day.

[Examples]

[0058]

The present invention will be described next in more detail with reference to examples; however, the invention is in no way limited to these examples.

In the following test examples, ripasudil monohydrochloride dihydrate can be produced in accordance with the method described in WO2006/057397, for example.

[0059]

[Test Example 1] Preservation test

Aqueous compositions of Example 1 and Comparative Example 1 containing the components in the quantities per 100 mL shown in Table 1 were prepared in accordance with a conventional method, and each housed in a container made of polypropylene.

The resulting aqueous compositions were preserved at 80°C for 1 week. The degree of discoloration (yellowing) after the preservation was evaluated by measuring the color difference (ΔYI) of the aqueous compositions before and after the preservation using a color difference meter (spectrophotometer, CM-700d: Konica Minolta Sensing, Inc.).

The results are shown in Table 1.

[0060]

[Table 1]

	Example 1	Comparative Example 1
Ripasudil Monohydrochloride Dihydrate	0.9792 g (0.8 g as the free form)	0.9792 g (0.8 g as the free form)
Bimatoprost	0.06 g	-
Anhydrous Sodium Dihydrogen Phosphate	0.4 g	0.4 g
Glycerin	2.136 g	2.136 g
Benzalkonium Chloride Concentrated Solution 50	0.002 mL	0.002 mL
Sodium Hydroxide	q.s. (pH6.0)	q.s. (pH6.0)
Purified Water	Total Amount 100 mL	Total Amount 100 mL
ΔYI	0.9	6.0

[0061]

As shown in the results set forth in Table 1, it was revealed that when bimatoprost is further incorporated in the aqueous composition containing ripasudil, the ΔYI value is significantly lowered in comparison with the case where the aqueous composition does not contain bimatoprost, and discoloration after high-temperature preservation is reduced.

[0062]

[Test Example 2] Preservation test No. 2

An aqueous composition of Example 2 containing the components in the quantities per 100 mL shown in Table 2 was prepared in accordance with a conventional method, and stored in a container made of polypropylene.

The resulting aqueous composition was preserved at 80°C for 1 week, and the degree of discoloration (yellowing) after the preservation was evaluated using the same method as in Test Example 1.

The results are shown in Table 2.

[0063]

[Table 2]

	Example 2
Ripasudil Monohydrochloride Dihydrate	0.9792 g (0.8 g as the free form)
Latanoprost	0.01 g
Anhydrous Sodium Dihydrogen Phosphate	0.4 g
Benzalkonium Chloride Concentrated Solution 50	0.002 mL
Sodium Hydroxide	q.s. (pH6.0)
Purified Water	Total Amount 100 mL
ΔYI	0.9

[0064]

As shown in the results set forth in Table 2, the ΔYI value was similarly low when latanoprost is further incorporated in the aqueous composition containing ripasudil.

[0065]

The foregoing results of Test Examples 1 and 2 revealed that when a prostaglandin typified by bimatoprost and latanoprost is further incorporated in

the aqueous composition containing the compound represented by Formula (1) typified by ripasudil or a salt thereof or a solvate of the compound or the salt thereof, discoloration (yellowing) is relatively difficult to occur even after preservation at high temperature, and excellent preservation stability can be achieved.

[0066]

[Test Example 3] Preservation test No. 3

Aqueous compositions of Example 3 and Comparative Example 2 containing the components in the quantities per 100 mL shown in Table 3 were prepared in accordance with a conventional method.

Each of the resulting aqueous compositions was preserved at -5°C, during which the presence or absence of crystal precipitation was visually evaluated periodically to determine for which aqueous composition earlier crystal precipitation would be observed. The aqueous composition for which earlier crystal precipitation was not observed was rated as "b", and the aqueous composition for which earlier crystal precipitation was observed was rated as "d".

The results are shown in Table 3.

[0067]

[Table 3]

	Example 3	Comparative Example 2
Ripasudil Monohydrochloride Dihydrate	0.9792 g (0.8 g as the free form)	0.9792 g (0.8 g as the free form)
Latanoprost	0.01 g	-
Anhydrous Sodium Dihydrogen Phosphate	0.4 g	0.4 g
Benzalkonium Chloride Concentrated Solution 50	0.002 mL	0.002 mL
Sodium Hydroxide	q.s. (pH6.0)	q.s. (pH6.0)
Purified Water	Total Amount 100 mL	Total Amount 100 mL
Crystal Precipitation	b	d

[0068]

As shown in the results set forth in Table 3, it was revealed that when latanoprost is further incorporated in the aqueous composition containing ripasudil, crystal precipitation during low-temperature preservation is suppressed in comparison with the case where the aqueous composition does not contain latanoprost.

[0069]

The foregoing test results revealed that when a prostaglandin typified by latanoprost is further incorporated in the aqueous composition containing the compound represented by Formula (1) typified by ripasudil or a salt thereof or a solvate of the compound or the salt thereof, precipitation of crystals is relatively difficult to occur even after preservation at low temperature, and excellent preservation stability can be achieved.

[0070]

[Production Examples 1 to 27]

Aqueous compositions containing the components in the quantities (amounts (g) per 100 mL of the aqueous composition) shown in Tables 4 to 6 can be produced in accordance with a conventional method.

[0071]

[Table 4]

	Production Example 1	Production Example 2	Production Example 3	Production Example 4	Production Example 5	Production Example 6	Production Example 7	Production Example 8	Production Example 9
Ripasudil Monohydrochloride Dihydrate (as the amount of the free form)	0.2	0.2	0.2	0.4	0.4	0.4	0.8	0.8	0.8
Latanoprost	0.005	-	-	-	0.005	-	-	0.005	-
Bimatoprost	-	0.01	0.03	-	-	-	-	-	0.03
Travoprost	-	-	-	0.004	-	-	-	-	-
Tafuprost	-	-	-	-	-	0.0015	0.003	-	-
Sodium Chloride	0.55	-	-	-	0.3	0.3	0.3	0.3	-
Glycerin	-	2	-	-	1	-	-	0.5	1
Propylene Glycol	-	-	2	-	-	1	-	0.5	1
Potassium Chloride	-	-	-	0.6	-	-	0.3	-	-
Boric Acid	-	-	-	-	-	-	-	-	-
Borax	-	-	-	-	-	-	-	-	-
Sodium Dihydrogenphosphate Monohydrate	0.4	0.4	0.4	-	-	0.4	0.4	0.4	0.4
Dibasic Sodium Phosphate Hydrate	-	-	-	-	-	-	-	q.s.	q.s.
Anhydrous Sodium Monohydrogen Phosphate	-	-	-	-	-	q.s.	q.s.	-	-
Potassium Dihydrogenphosphate	-	-	-	0.4	0.4	-	-	-	-
Sodium Hydroxide	q.s.	q.s.	q.s.	q.s.	q.s.	-	-	-	-
Trometamol	-	-	-	-	-	-	-	-	-
Hydrochloric Acid	-	-	-	-	-	-	q.s.	q.s.	q.s.
Citric Acid Hydrate	0.1	-	-	-	-	0.1	-	-	-
Sodium Acetate Hydrate	-	0.1	-	-	-	0.1	-	-	-
Sodium Edetate	-	-	-	0.1	-	-	0.1	-	-
Benzalkonium Chloride	0.001	0.005	-	0.001	0.005	0.01	0.001	0.005	-
Benzethonium Chloride	-	-	-	-	-	-	-	-	0.01
Methyl Parahydroxybenzoate	-	-	0.01	-	-	-	0.01	-	-
Propyl Parahydroxybenzoate	-	-	0.01	-	-	-	0.01	-	-
Chlorbutanol	-	-	-	0.2	-	-	-	0.2	-
Polysorbate 80	0.3	-	-	0.3	0.3	-	-	0.3	0.3
Polyoxyethylene Castor Oil 60	-	0.3	-	0.3	-	0.3	-	0.3	0.3
Polyethylene Glycol Monostearate	-	-	1.5	1.5	-	-	1.5	-	1.5
Purified Water	Total Amount 100 mL	Total Amount 100 mL	Total Amount 100 mL	Total Amount 100 mL	Total Amount 100 mL	Total Amount 100 mL	Total Amount 100 mL	Total Amount 100 mL	Total Amount 100 mL
pH	5	5	6	6	6.5	6.5	4.5	4.5	4

[0072]

[Table 5]

	Production Example 10	Production Example 11	Production Example 12	Production Example 13	Production Example 14	Production Example 15	Production Example 16	Production Example 17	Production Example 18
Ripasudil Monohydrochloride Dihydrate (as the amount of the free form)	0.2	0.2	0.2	0.4	0.4	0.4	0.8	0.8	0.8
Latanoprost	0.005	-	-	-	0.005	-	-	0.005	-
Bimatoprost	-	0.01	0.03	-	-	-	-	-	0.03
Travoprost	-	-	-	0.004	-	-	-	-	-
Tafuprost	-	-	-	-	-	0.0015	0.003	-	-
Sodium Chloride	0.65	-	-	-	0.3	0.3	0.3	0.3	-
Glycerin	-	2	-	-	1	-	-	0.5	1
Propylene Glycol	-	-	2	-	-	1	-	0.5	1
Potassium Chloride	-	-	-	0.6	-	-	0.3	-	-
Boric Acid	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Borax	-	-	-	-	q.s.	q.s.	-	-	-
Sodium Dihydrogenphosphate Monohydrate	-	-	-	-	-	-	-	-	-
Dibasic Sodium Phosphate Hydrate	-	-	-	-	-	-	-	-	-
Anhydrous Sodium Monohydrogen Phosphate	-	-	-	-	-	-	-	-	-
Potassium Dihydrogenphosphate	-	-	-	-	-	-	-	-	-
Sodium Hydroxide	q.s.	q.s.	q.s.	q.s.	-	-	-	-	-
Trometamol	-	-	-	-	-	-	-	-	-
Hydrochloric Acid	-	-	-	-	-	-	-	-	-
Citric Acid Hydrate	0.1	-	-	-	-	0.1	q.s.	q.s.	q.s.
Sodium Acetate Hydrate	-	0.1	-	-	-	0.1	-	-	-
Sodium Edetate	-	-	-	0.1	-	-	0.1	-	-
Benzalkonium Chloride	0.001	0.005	-	0.001	0.005	0.01	0.001	0.005	-
Benzethonium Chloride	-	-	-	-	-	-	-	-	0.01
Methyl Parahydroxybenzoate	-	-	0.01	-	-	-	0.01	-	-
Propyl Parahydroxybenzoate	-	-	0.01	-	-	-	0.01	-	-
Chlorobutanol	-	-	-	0.2	-	-	-	0.2	-
Polysorbate 80	0.3	-	-	0.3	0.3	-	-	0.3	0.3
Polyoxyethylene Castor Oil 60	-	0.3	-	0.3	-	0.3	-	0.3	0.3
Polyethylene Glycol Monostearate	-	-	1.5	1.5	-	-	1.5	-	1.5
Purified Water	Total Amount 100 mL	Total Amount 100 mL	Total Amount 100 mL	Total Amount 100 mL	Total Amount 100 mL	Total Amount 100 mL	Total Amount 100 mL	Total Amount 100 mL	Total Amount 100 mL
pH	5	5	6	6	6.5	6.5	4.5	4.5	4

[0073]

[Table 6]

	Production Example 19	Production Example 20	Production Example 21	Production Example 22	Production Example 23	Production Example 24	Production Example 25	Production Example 26	Production Example 27
Ripasudil Monohydrochloride Dihydrate (as the amount of the free form)	0.2	0.2	0.2	0.4	0.4	0.4	0.8	0.8	0.8
Latanoprost	0.005	-	-	-	0.005	-	-	0.005	-
Bimatoprost	-	0.01	0.03	-	-	-	-	-	0.03
Travoprost	-	-	-	0.004	-	-	-	-	-
Tafuprost	-	-	-	-	-	0.0015	0.003	-	-
Sodium Chloride	0.65	-	-	-	0.3	0.3	0.3	0.3	-
Glycerin	-	2	-	-	1	-	-	0.5	1
Propylene Glycol	-	-	2	-	-	1	-	0.5	1
Potassium Chloride	-	-	-	0.6	-	-	0.3	-	-
Boric Acid	-	-	-	-	-	-	-	-	-
Borax	-	-	-	-	-	-	-	-	-
Sodium Dihydrogenphosphate Monohydrate	-	-	-	-	-	-	-	-	-
Dibasic Sodium Phosphate Hydrate	-	-	-	-	-	-	-	-	-
Anhydrous Sodium Monohydrate Phosphate	-	-	-	-	-	-	-	-	-
Potassium Dihydrogenphosphate	-	-	-	-	-	-	-	-	-
Sodium Hydroxide	-	-	-	-	-	-	-	-	-
Trimetamol	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Hydrochloric Acid	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Citric Acid Hydrate	0.1	-	-	-	-	0.1	-	-	-
Sodium Acetate Hydrate	-	0.1	-	-	-	0.1	-	-	-
Sodium Edetate	-	-	-	0.1	-	-	0.1	-	-
Benzalkonium Chloride	0.001	0.005	-	0.001	0.005	0.01	0.001	0.005	-
Benzethonium Chloride	-	-	-	-	-	-	-	-	0.01
Methyl Parahydroxybenzoate	-	-	0.01	-	-	-	0.01	-	-
Propyl Parahydroxybenzoate	-	-	0.01	-	-	-	0.01	-	-
Chlorobutanol	-	-	-	0.2	-	-	-	0.2	-
Polysorbate 80	0.3	-	-	0.3	0.3	-	-	0.3	0.3
Polyoxyethylene Castor Oil 60	-	0.3	-	0.3	-	0.3	-	0.3	0.3
Polyethylene Glycol Monostearate	-	-	1.5	1.5	-	-	1.5	-	1.5
Purified Water	Total Amount 100 mL	Total Amount 100 mL	Total Amount 100 mL	Total Amount 100 mL	Total Amount 100 mL	Total Amount 100 mL	Total Amount 100 mL	Total Amount 100 mL	Total Amount 100 mL
pH	5	5	6	6	6.5	6.5	4.5	4.5	4

[0074]

[Production Examples 28 to 54]

Aqueous compositions of Production Examples 28 to 54 can be produced in accordance with a conventional method as in Production Examples 1 to 27, except that instead of ripasudil monohydrochloride dihydrate, an equal amount of 4-bromo-5-{[(2S)-2-methyl-1,4-diazepan-1-yl]sulfonyl}isoquinoline is used.

[0075]

[Production Examples 55 to 108]

Pharmaceutical preparations of Production Examples 55 to 108 can be produced in accordance with a conventional method by storing the aqueous compositions of Production Examples 1 to 54 in a container made of polypropylene for eye drops.

[0076]

[Production Examples 109 to 162]

Pharmaceutical preparations of Production Examples 109 to 162 can be produced in accordance with a conventional method by storing the aqueous compositions of Production Examples 1 to 54 in a container made of polyethylene for eye drops.

[Industrial Applicability]

[0077]

In accordance with the present invention, aqueous compositions or pharmaceutical preparations having excellent preservation stability can be provided, which

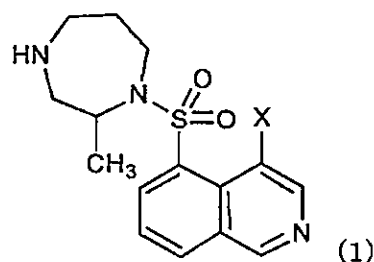
can be advantageously used in the pharmaceutical industry,
for example.

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Claims

[Claim 1]

An aqueous composition comprising a compound represented by Formula (1):



wherein X represents a halogen atom,

or a salt thereof, or a solvate of the compound or the salt thereof, and a prostaglandin.

[Claim 2]

The aqueous composition according to claim 1, wherein

the compound represented by Formula (1) is ripasudil.

[Claim 3]

The aqueous composition according to claim 1 or 2, wherein the prostaglandin is one or more selected from the group consisting of tafluprost, travoprost, bimatoprost, latanoprost, a salt of tafluprost, a salt of travoprost, a salt of bimatoprost, a salt of latanoprost, a solvate of tafluprost or the salt thereof, a solvate of travoprost or the salt thereof, a solvate of bimatoprost or the salt thereof, and a solvate of latanoprost or the salt thereof.

[Claim 4]

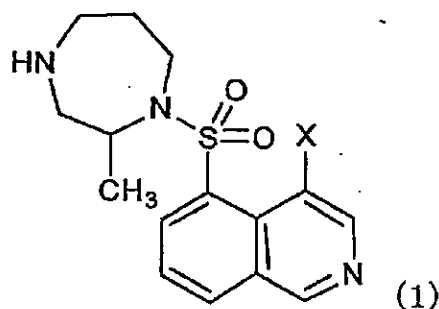
A pharmaceutical preparation obtained by storing the aqueous composition according to any one of claims 1 to 3 in a container made of polyolefin-based resin.

[Claim 5]

The pharmaceutical preparation according to claim 4, wherein the polyolefin-based resin is polypropylene.

[Claim 6]

A method for reducing discoloration of an aqueous composition, the method comprising the step of incorporating a prostaglandin in an aqueous composition comprising a compound represented by Formula (1):



wherein X represents a halogen atom,
or a salt thereof, or a solvate of the compound or
the salt thereof.

[Claim 7]

The method according to claim 6, wherein
the compound represented by Formula (1) is ripasudil.

[Claim 8]

The method according to claim 6 or 7, wherein the prostaglandin is one or more selected from the group consisting of tafluprost, travoprost, bimatoprost, latanoprost, a salt of tafluprost, a salt of travoprost,

a salt of bimatoprost, a salt of latanoprost, a solvate of tafluprost or the salt thereof, a solvate of travoprost or the salt thereof, a solvate of bimatoprost or the salt thereof, and a solvate of latanoprost or the salt thereof.