

SPECIFICATION

OPHTHALMIC SOLUTION COMPRISING EPINASTINE

5 TECHNICAL FIELD

[0001] The present invention relates to an ophthalmic solution comprising epinastine or a salt thereof in a concentration of over 0.075% (w/v) wherein the ophthalmic solution is substantially free of preservatives and ingredients with preservative efficacy (hereinafter also referred to as "the ophthalmic solution of the present invention").

BACKGROUND ART

15 [0002] Ophthalmic solutions should have a certain or higher level of preservative efficacy to prevent microorganisms such as bacteria from the propagation associated with repeated uses thereof. Ophthalmic solutions typically comprise a preservative. For example, 20 benzalkonium chloride is used as a typical preservative for ophthalmic solutions because it is water-soluble and chemically stable, and also has higher preservative efficacy as compared to other preservatives. On the other hand, benzalkonium chloride has cytotoxicity and can induce 25 corneal epithelium disorder if the exposure is increased.

Hence, benzalkonium chloride cannot be used for patients with hypersensitivity to it and patients suffering from severe corneal epithelium disorder.

[0003] Alesion® 0.05% ophthalmic solution, which is
5 currently marketed in Japan, is an ophthalmic solution comprising epinastine hydrochloride as an active ingredient, and comprises other ingredients with preservative efficacy (boric acid and edetic acid (EDTA)) instead of a commonly-used preservative such as benzalkonium chloride (Non-Patent
10 Document 1). That is, in order to repeatedly use an ophthalmic solution comprising epinastine or a salt thereof, the ophthalmic solution may not necessarily comprise a preservative such as benzalkonium chloride, but it is understood that it is necessary to secure preservative
15 efficacy using other ingredient with preservative efficacy instead of the preservative. An ophthalmic solution comprising epinastine or a salt thereof wherein the ophthalmic solution is free of both preservatives and ingredients with preservative efficacy is not known at all.

[0004] Among ophthalmic solutions which have been
20 marketed, an ophthalmic solution comprising neither preservatives nor ingredients with preservative efficacy have already been known. However, the ophthalmic solution is a unit-dose (single-use) ophthalmic solution or an
25 ophthalmic solution filled in a preservative-free container

(container with a special structure for producing preservative efficacy). An ophthalmic solution whose active ingredient itself can produce preservative efficacy has not been reported. That is, it is not known that
5 epinastine or a salt thereof itself can produce preservative efficacy.

PRIOR ART DOCUMENTS

NON-PATENT DOCUMENTS

10 [0005]

Non-Patent Document 1: Alesion® 0.05% ophthalmic solution, Package insert

SUMMARY OF INVENTION

15 (PROBLEM TO BE SOLVED BY THE INVENTION)

[0006] An object of the present invention is to provide an ophthalmic solution comprising epinastine or a salt thereof wherein the ophthalmic solution is substantially free of preservatives and ingredients with preservative
20 efficacy.

(MEANS FOR SOLVING THE PROBLEMS)

[0007] The present inventors have extensively studied to develop an ophthalmic solution comprising epinastine or a
25 salt thereof wherein the ophthalmic solution is free of

preservatives and ingredients with preservative efficacy or comprises them in a less content than usual, and then have found that an ophthalmic solution comprising epinastine or a salt thereof in a concentration of over 0.075% (w/v) can
5 produce good preservative efficacy even if the solution is substantially free of preservatives and ingredients with preservative efficacy. Based upon the new findings, the present invention has been completed.

Specifically, the present invention provides the
10 following embodiments.

(1) An ophthalmic solution comprising epinastine or a salt thereof in a concentration of over 0.075% (w/v) wherein the ophthalmic solution is substantially free of preservatives and ingredients with preservative efficacy.

15 (2) The ophthalmic solution of (1), wherein the concentration of epinastine or a salt thereof is 0.1% to 5.0% (w/v).

(3) The ophthalmic solution of (1) or (2), wherein epinastine or a salt thereof is epinastine hydrochloride.

20 (4) The ophthalmic solution of (1), wherein the preservatives and ingredients with preservative efficacy are at least one selected from the group consisting of benzalkonium chloride, chlorhexidine or a salt thereof, boric acid, borax, and edetic acid or a salt thereof.

25 (5) An ophthalmic solution comprising only epinastine or a

salt thereof in a concentration of over 0.075% (w/v) as an active ingredient and only a buffering agent, a tonicity agent and a pH adjuster as an additive.

(6) The ophthalmic solution of (5), wherein the
5 concentration of epinastine or a salt thereof is 0.1% to 5.0% (w/v).

(7) The ophthalmic solution of (5) or (6), wherein epinastine or a salt thereof is epinastine hydrochloride.

(8) The ophthalmic solution of any one of (5) to (7),
10 wherein the buffering agent is phosphoric acid or a salt thereof.

(9) The ophthalmic solution of any one of (5) to (8), wherein the tonicity agent is an ionic tonicity agent.

(10) The ophthalmic solution of any one of (1) to (9) which
15 is a multi-dose ophthalmic solution.

(11) A method of providing preservative efficacy to an ophthalmic solution comprising epinastine or a salt thereof wherein the ophthalmic solution is substantially free of preservatives and ingredients with preservative efficacy,
20 by composing epinastine or the salt thereof in a concentration of over 0.075% (w/v).

(12) A method of maintaining preservative efficacy in an ophthalmic solution comprising epinastine or a salt thereof wherein the ophthalmic solution is substantially free of
25 preservative and ingredient with preservative efficacy, by

composing epinastine or the salt thereof in a concentration of over 0.075% (w/v).

Each feature of the above (1) to (12) can be optionally selected and combined two or more.

5 Furthermore, the present invention also provides the following embodiments.

(13) A method of treating and/or preventing allergic conjunctivitis, which comprises administering a therapeutically effective amount of the ophthalmic solution
10 of any one of (1) to (10) to a patient in need thereof.

(14) The ophthalmic solution of any one of (1) to (10) for use in treating and/or preventing allergic conjunctivitis.

(EFFECTS OF THE INVENTION)

15 [0008] According to the present invention, an ophthalmic solution comprising epinastine or a salt thereof with preservative efficacy can be provided even if neither preservatives nor ingredients with preservative efficacy are used.

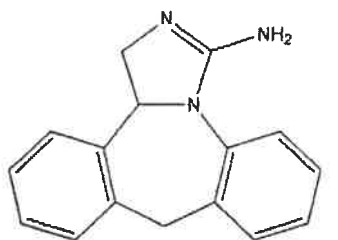
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DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0009] Hereinafter, the present invention is explained in detail.

[0010] "Epinastine" as used herein is a compound
25 represented by chemical name: (±)-3-Amino-9,13b-dihydro-1H-

dibenz[c,f]imidazo[1,5-a]azepine, and also the following formula:



[0011] Epinastine in the ophthalmic solution of the
5 present invention may be in a salt form, and it is not particularly limited as long as the salt is a pharmaceutically acceptable salt. Examples thereof include salts with an inorganic acid, an organic acid, and others.

Examples of the inorganic acid include hydrochloric
10 acid, hydrobromic acid, hydroiodic acid, nitric acid, sulfuric acid, phosphoric acid, and others.

Examples of the organic acid include acetic acid, oxalic acid, fumaric acid, maleic acid, succinic acid, malic acid, citric acid, tartaric acid, adipic acid,
15 gluconic acid, glucoheptonic acid, glucuronic acid, terephthalic acid, methanesulfonic acid, alanine, lactic acid, hippuric acid, 1,2-ethanedisulfonic acid, isethionic acid, lactobionic acid, oleic acid, gallic acid, pamoic acid, polygalacturonic acid, stearic acid, tannic acid,
20 trifluoromethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, lauryl sulfate, methyl sulfate, naphthalenesulfonic acid, sulfosalicylic acid, and others.

Particularly preferably, the salt of epinastine is monohydrochloride (epinastine hydrochloride).

[0012] Epinastine or a salt thereof as used herein may be in the form of a hydrate or a solvate.

5 [0013] The adequate content of epinastine or a salt thereof as used herein is over 0.075% (w/v). Also, the concentration thereof may be 0.085% (w/v) or more or 0.1% (w/v) or more. The upper limit is not limited as long as it is the concentration that is acceptable as ophthalmic
10 formulations. For example, the upper limit is 5% (w/v). The adequate content of epinastine or a salt thereof is preferably 0.1 to 5.0% (w/v), more preferably 0.1 to 3.0% (w/v), furthermore preferably 0.1 to 1.0% (w/v), and particularly preferably 0.1 to 0.5% (w/v) or 0.1 to 0.3%
15 (w/v). Also, the content thereof may be 0.1% (w/v), 0.2% (w/v), 0.3% (w/v), 0.4% (w/v), or 0.5% (w/v).

When the ophthalmic solution of the present invention comprises a salt of epinastine, the values mean the content of the salt. The term "% (w/v)" means the mass (g) of an
20 object ingredient (herein, epinastine or a salt thereof) in 100 mL of the ophthalmic solution. Hereinafter, the same shall apply to the followings unless otherwise specified.

[0014] Examples of the preservatives as used herein include benzalkonium chloride, benzalkonium bromide,
25 benzethonium chloride, chlorhexidine or a salt thereof,

sorbic acid or a salt thereof, methyl para-hydroxybenzoate, propyl para-hydroxybenzoate, chlorobutanol, and others.

Examples of chlorhexidine or a salt thereof include chlorhexidine gluconate, chlorhexidine hydrochloride, chlorhexidine acetate, and others.

Examples of sorbic acid or a salt thereof include sodium sorbate, potassium sorbate, and others.

[0015] Examples of the ingredients with preservative efficacy as used herein include boric acid, borax, edetic acid or a salt thereof, and others.

Examples of edetic acid or a salt thereof include monosodium edetate, disodium edetate, tetrasodium edetate, and others.

[0016] The term "free of preservatives and ingredients with preservative efficacy" as used herein means that an ophthalmic solution comprises none of the "preservatives and ingredients with preservative efficacy" or comprises the "preservatives and ingredients with preservative efficacy" in an amount which does not meet the requirement defined in the preservatives-effectiveness tests described in the Japanese Pharmacopoeia 17th Edition. The above "amount that does not meet the requirement defined in the preservatives-effectiveness tests described in the Japanese Pharmacopoeia 17th Edition" means an amount for producing not preservative efficacy of the preservatives and

ingredients with preservative efficacy but another effect thereof. For example, when the preservatives and ingredients with preservative efficacy are EDTA, the amount thereof may be approximately 0.01% (w/v) or 0.02% (w/v).

5 In such case, EDTA is added into an ophthalmic solution to produce not preservative efficacy thereof but stabilizing effect thereof. Also, when the preservatives and ingredients with preservative efficacy are boric acid, the amount thereof may be approximately 0.01% (w/v) or 0.02%

10 (w/v). In such case, boric acid is added into an ophthalmic solution to produce not preservative efficacy thereof but buffering effect thereof. The term "substantially" as used herein indicates that the feature is not changed. Hence, the term "substantially free of preservatives and ingredients with preservative efficacy" as used herein means that an ophthalmic solution comprises none of "preservatives and ingredients with preservative efficacy" or comprises the "preservatives and ingredients with preservative efficacy" in an amount that does not meet
15 the requirement defined in the preservatives-effectiveness tests described in the Japanese Pharmacopoeia 17th Edition when it is not intended to produce preservative efficacy.

[0017] The term "multi-dose ophthalmic solution" as used herein means an ophthalmic solution filled in a multi-dose
25 container. The multi-dose container is designed so that a

cap can be freely opened and closed for multiple uses of an ophthalmic solution. The multi-dose container can be used for a given period of time after first opening, and also can be easily carried. The size and shape of the container body as used herein are not particularly limited. The ophthalmic solution of the present invention may be placed in a unit-dose (single-use) container. More preferably, the ophthalmic solution is placed in a multi-dose container because it provides preservative efficacy. A container with a special structure for producing preservative efficacy such as backflow prevention function, for example, a PFMD (Preservative Free Multi Dose) container is not encompassed in the multi-dose container. The material of such container is not particularly limited. A commonly-used container such as a container made of polyethylene (PE), polypropylene (PP), or polyethylene terephthalate (PET) may be used.

[0018] The ophthalmic solution of the present invention may completely dissolve or partially suspend ingredients therein. More preferably, the ophthalmic solution is in the solution state that all ingredients are completely dissolved.

[0019] The ophthalmic solution of the present invention may comprise a buffering agent available as pharmaceutical additives. Examples thereof include phosphoric acid or a

salt thereof, citric acid or a salt thereof, acetic acid or a salt thereof, carbonic acid or a salt thereof, tartaric acid or a salt thereof, ϵ -aminocaproic acid, trometamol, and others. They may be in the form of a hydrate or a solvate.

Examples of phosphoric acid or a salt thereof include sodium phosphate, sodium dihydrogen phosphate, disodium hydrogen phosphate, potassium phosphate, potassium dihydrogen phosphate, dipotassium hydrogen phosphate, and others. They may be in form of a hydrate.

Examples of citric acid or a salt thereof include sodium citrate, disodium citrate, and others. They may be in the form of a hydrate.

Examples of acetic acid or a salt thereof include sodium acetate, potassium acetate, and others. They may be in the form of a hydrate.

Examples of carbonic acid or a salt thereof include sodium carbonate, sodium hydrogen carbonate, and others. They may be in the form of a hydrate.

Examples of tartaric acid or a salt thereof include sodium tartrate, potassium tartrate, and others. They may be in the form of a hydrate.

The buffering agent in the ophthalmic solution of the present invention is more preferably phosphoric acid or a salt thereof, particularly preferably sodium dihydrogen

phosphate, disodium hydrogen phosphate or a hydrate thereof. Two or more of the buffering agents may be used in combination.

5 The content of the buffering agent in the ophthalmic solution of the present invention can be varied depending on the type of the buffering agent. The content thereof is preferably 0.001 to 10% (w/v), more preferably 0.01 to 5% (w/v), furthermore preferably 0.1 to 3% (w/v), most preferably 0.2 to 1.5% (w/v).

10 [0020] The ophthalmic solution of the present invention may comprise a tonicity agent available as pharmaceutical additives. Examples thereof include an ionic tonicity agent, a non-ionic tonicity agent, and others.

15 Examples of the ionic tonicity agent include sodium chloride, potassium chloride, calcium chloride, magnesium chloride, and others.

Examples of the non-ionic tonicity agent include glycerin, propylene glycol, polyethylene glycol, sorbitol, mannitol, trehalose, maltose, sucrose, and others.

20 The tonicity agent in the ophthalmic solution of the present invention is more preferably an ionic tonicity agent, particularly preferably sodium chloride. Two or more of the tonicity agents may be used in combination.

The content of the tonicity agent in the ophthalmic
25 solution of the present invention can be varied depending

on the type of the tonicity agent. The content thereof is preferably 0.001 to 10% (w/v), more preferably 0.01 to 5% (w/v), furthermore preferably 0.1 to 1% (w/v), most preferably 0.2 to 0.5% (w/v).

5 The osmotic pressure ratio of the ophthalmic solution of the present invention is not limited as long as it is within a range acceptable for ophthalmic formulations. The osmotic pressure thereof is, for example, 0.5 to 2.0, preferably 0.7 to 1.6, more preferably 0.8 to 1.4, and
10 furthermore preferably 0.9 to 1.2.

[0021] The ophthalmic solution of the present invention may comprise a pH adjuster available as pharmaceutical additives. The pH adjuster is, for example, an acid or a base. Examples of the acid include hydrochloric acid,
15 phosphoric acid, citric acid, acetic acid, and others. Examples of the base include sodium hydroxide, potassium hydroxide, sodium carbonate, sodium hydrogen carbonate, and others.

 The pH of the ophthalmic solution of the present
20 invention is not limited as long as it is within a range acceptable for ophthalmic formulations. The pH thereof is preferably 4.0 to 8.0, more preferably 6.0 to 8.0, furthermore preferably 6.5 to 7.5, and particularly preferably 6.7 to 7.3. Also, the pH thereof may be 6.7,
25 6.8, 6.9, 7.0, 7.1, 7.2, or 7.3.

[0022] The ophthalmic solution of the present invention may comprise one or more additives acceptable for ophthalmic formulations (except for preservatives and ingredients with preservative efficacy) besides the above-described buffering agent, tonicity agent, and pH adjuster. Examples thereof include a solubilizing agent, a stabilizing agent, an antioxidant, a thickening agent, and others. In addition, unless otherwise specified, the ophthalmic solution may comprise any active ingredient used for ophthalmic formulations other than epinastine or salt thereof.

Examples of the solubilizing agent include polyoxyethylene hydrogenated castor oil, povidone, polysorbate 80, and others. Examples of the stabilizing agent include povidone, polysorbate 80, and others. Examples of the antioxidant include dibutylhydroxytoluene, sodium sulfite, and others. Examples of the thickening agent include carboxyvinyl polymer, hydroxyethyl cellulose, and others. They can be added in the range acceptable for ophthalmic formulations. Each additive may be added in an amount of 2% or less, 0.2% or less, 0.02% or less, or 0.002% or less.

[0023] The ophthalmic solution of the present invention is useful as an agent for treating allergic conjunctivitis.

[0024] When the ophthalmic solution of the present

invention is administered, its dose and administration is not particularly limited as long as it is sufficient to exhibit a desired efficacy. The ophthalmic solution can be administered at a dose of 1 drop a time, 1 to 10 times daily, preferably 2 to 6 times daily, more preferably 2 to 4 times, furthermore 2 times or 4 times daily. Also, the ophthalmic solution can be used with wearing contact lenses.

EXAMPLES

[0025] Hereinafter, the present invention is illustrated in more detail in Formulation Examples and the results of Preservative Efficacy Test. The present invention, however, is not intended to be limited to them by any means.

[0026]

[Formulation Examples]

Typical formulation examples of the present invention are shown below. The amount of each ingredient formulated in the following formulation examples is the content in 1 mL of the formulation.

[0027]

Formulation Example 1

In multi-dose container (1 mL)

Epinastine hydrochloride	1 mg
Sodium dihydrogen phosphate	3 mg
Sodium chloride	5 mg

Dilute hydrochloric acid	Appropriate quantity
Sodium hydroxide	Appropriate quantity
Purified water	Appropriate quantity

[0028]

5 Formulation Example 2

In multi-dose container (1 mL)

Epinastine hydrochloride	3 mg
Sodium dihydrogen phosphate	3 mg
Disodium hydrogen phosphate	12 mg
10 Sodium chloride	4 mg
Dilute hydrochloric acid	Appropriate quantity
Sodium hydroxide	Appropriate quantity
Purified water	Appropriate quantity

[0029]

15 Preservative Efficacy Test (1)

This test was performed according to the preservatives-effectiveness tests described in the Japanese Pharmacopoeia Seventeenth Edition.

20 1. Preparation of test formulations

Epinastine (50 mg), sodium dihydrogen phosphate (25 mg), disodium hydrogen phosphate hydrate (122 mg), and sodium chloride (40 mg) were dissolved in water and the mixture was sterilized by filtration, and then a pH
25 adjuster and water were added thereto so that the total

amount was 10 mL to prepare the formulation of Example 1.

[0030]

Example 1

In 1 mL of the formulation

5	Epinastine hydrochloride	5 mg
	Sodium dihydrogen phosphate	2.5 mg
	Disodium hydrogen phosphate hydrate	12.2 mg
	Sodium chloride	4 mg
	Dilute hydrochloric acid	Appropriate quantity
10	Sodium hydroxide	Appropriate quantity
	Purified water	Appropriate quantity
	pH	6.7

[0031] According to a similar process to that of Example 1, the formulations of Examples 2-4 and Comparative Examples 1-2 were prepared.

[0032]

Example 2

In 1 mL of the formulation

	Epinastine Hydrochloride	50 mg
20	Sodium dihydrogen phosphate	2.5 mg
	Disodium hydrogen phosphate hydrate	12.2 mg
	Dilute Hydrochloric Acid	Appropriate quantity
	Sodium Hydroxide	Appropriate quantity
	Purified Water	Appropriate quantity
25	pH	6.7

[0033]

Example 3

In 1 mL of the formulation

	Epinastine Hydrochloride	1 mg
5	Sodium dihydrogen phosphate	2.5 mg
	Disodium hydrogen phosphate hydrate	12.2 mg
	Sodium chloride	4.7 mg
	Dilute hydrochloric acid	Appropriate quantity
	Sodium hydroxide	Appropriate quantity
10	Purified water	Appropriate quantity
	pH	6.7

[0034]

Example 4

In 1 mL of the formulation

15	Epinastine Hydrochloride	2 mg
	Sodium dihydrogen phosphate	2.5 mg
	Disodium hydrogen phosphate hydrate	12.2 mg
	Sodium chloride	4.5 mg
	Dilute hydrochloric acid	Appropriate quantity
20	Sodium hydroxide	Appropriate quantity
	Purified water	Appropriate quantity
	pH	6.7

[0035]

Comparative Example 1

25 In 1 mL of the formulation

	Epinastine hydrochloride	0.5 mg
	Sodium dihydrogen phosphate	2.5 mg
	Disodium hydrogen phosphate hydrate	12.2 mg
	Sodium chloride	5 mg
5	Dilute hydrochloric acid	Appropriate quantity
	Sodium hydroxide	Appropriate quantity
	Purified water	Appropriate quantity
	pH	6.7

[0036]

10 Comparative Example 2

In 1 mL of the formulation

	Epinastine hydrochloride	0.75 mg
	Sodium dihydrogen phosphate	2.5 mg
	Disodium hydrogen phosphate hydrate	12.2 mg
15	Sodium chloride	4.7 mg
	Dilute hydrochloric acid	Appropriate quantity
	Sodium hydroxide	Appropriate quantity
	Purified water	Appropriate quantity
	pH	6.7

20 [0037]

2. Test Method

The following microorganisms were used as inoculum

Bacteria:

Escherichia Coli, *Escherichia Coli* ATCC 8739 (also
 25 referred to as *E. coli*)

Pseudomonas aeruginosa, *Pseudomonas aeruginosa* ATCC 9027
(also referred to as *P. aeruginosa*)

Staphylococcus aureus, *Staphylococcus aureus* ATCC 6538
(also referred to as *S. aureus*)

5 Yeast and Fungi:

Candida, *Candida albicans* ATCC 10231 (also referred to as
C. albicans)

Aspergillus niger, *Aspergillus brasiliensis* ATCC16404
(also referred to as *A. brasiliensis*)

10 [0038] A solution of each inoculum was inoculated to
each test sample comprising each formulation so that the
concentration of the solution in the test sample ranged
from 10^5 to 10^6 cfu/mL (in all of the above 5
microorganisms). Specifically, the solution of each
15 microorganism was prepared in a concentration of 10^7 to 10^8
cfu/mL. The prepared solution was inoculated to each test
sample comprising each formulation of Examples 1-4 and
Comparative Examples 1-2 so that the concentration of the
solution in the test sample ranged from 10^5 to 10^6 cfu/mL,
20 and then the resulting solution was homogeneously mixed to
prepare a sample. The prepared samples were stored at 20
to 25°C in a place away from light, and 1 mL of each sample
was collected with a micropipette at each sampling point (7
days later, 14 days later, or 28 days later) to measure the
25 number of viable microorganisms. At each sampling point,

the cap of the container filled in the sample solution was opened, sampling was performed, and then the cap was closed.
[0039]

3. Test Results and Discussion

5 The test results are shown in Tables 1 and 2. The results of Tables 1 and 2 are the common logarithmic value of the ratio (B/A) of the number (B) of microorganisms at the time of inoculation to the number (A) of microorganisms when the viable microorganisms is measured. For example,
10 when the value is "1", it shows that the measured number of viable microorganisms decreased to 10% of the number of inoculated microorganisms.

 For determination of conformity or non-conformity in the test, when the value for bacterial species (*E. coli*, *P. aeruginosa*, *S. aureus*) is 1.0 or more 7 days after
15 inoculation and 3.0 or more 14 days or 28 days after inoculation as well as the value 7 days after inoculation for fungal species (*C. albicans*, *A. brasiliensis*) is not reduced as compared to the value 14 days or 28 days after
20 inoculation, it was determined as being conformity.

[0040]

[Table 1]

Microorganisms	Sampling Time	Comparative Example 1	Example 1	Example 2
E. Coli	7 days later	4.5	4.5	4.5
	14 days later	4.5	4.5	4.5
P. aeruginosa	7 days later	2.0	4.8	4.8
	14 days later	2.0	4.8	4.8
S. aureus	7 days later	1.7	4.7	4.7
	14 days later	4.7	4.7	4.7
C. albicans	7 days later	3.3	4.6	4.6
	14 days later	4.6	4.6	4.6
A. brasiliensis	7 days later	0.5	2.0	2.0
	14 days later	0.7	2.6	3.0
Determination		Non-conformity	Conformity	Conformity

[0041]

[Table 2]

Microorganisms	Sampling Time	Comparative Example 2	Example 3	Example 4
E. Coli	7 days later	>4.4	>4.4	>4.4
	28 days later	>4.4	>4.4	>4.4
P. aeruginosa	7 days later	3.9	>5.0	>5.0
	28 days later	2.9	>5.0	>5.0
S. aureus	7 days later	>4.7	>4.7	>4.7
	28 days later	>4.7	>4.7	4.7
C. albicans	7 days later	3.3	3.2	3.7
	28 days later	>4.6	>4.6	>4.6
A. brasiliensis	7 days later	0.2	0.5	0.4
	28 days later	2.0	1.8	2.7
Determination		Non-conformity	Conformity	Conformity

[0042] As shown in Tables 1 and 2, the formulations of Examples 1-4 comprising epinastine or a salt thereof produced good preservative efficacy for all of the microorganisms without any preservatives and ingredients with preservative efficacy. On the other hand, it was shown that the formulations of Comparative Examples 1 and 2 did not produce good preservative efficacy. As a result, it was suggested that the ophthalmic solution comprising epinastine or a salt thereof in a concentration of over 0.075% (w/v) of the present invention could be used with

repeatedly opening and closing a container as a multi-dose ophthalmic solution even if neither preservatives nor ingredients with preservative efficacy are used.

5 INDUSTRIAL APPLICABILITY

[0043] The present invention provides an ophthalmic solution comprising epinastine or a salt thereof in a concentration of over 0.075% (w/v) wherein the ophthalmic solution is substantially free of preservatives and
10 ingredients with preservative efficacy.

CLAIMS

1. An ophthalmic solution comprising epinastine or a salt thereof in a concentration of over 0.075% (w/v) wherein the ophthalmic solution is substantially free of preservatives and ingredients with preservative efficacy.
2. The ophthalmic solution of claim 1, wherein the concentration of epinastine or a salt thereof is 0.1% to 5.0% (w/v).
3. The ophthalmic solution of claim 1 or 2, wherein epinastine or a salt thereof is epinastine hydrochloride.
4. The ophthalmic solution of claim 1, wherein the preservatives and ingredients with preservative efficacy are at least one selected from the group consisting of benzalkonium chloride, chlorhexidine or a salt thereof, boric acid, borax, and edetic acid or a salt thereof.
5. An ophthalmic solution comprising only epinastine or a salt thereof in a concentration of over 0.075% (w/v) as an active ingredient and only a buffering agent, a tonicity agent and a pH adjuster as an additive.

6. The ophthalmic solution of claim 5, wherein the concentration of epinastine or a salt thereof is 0.1% to 5.0% (w/v).

5 7. The ophthalmic solution of claim 5 or 6, wherein epinastine or a salt thereof is epinastine hydrochloride.

8. The ophthalmic solution of any one of claims 5 to 7, wherein the buffering agent is phosphoric acid or a salt thereof.
10

9. The ophthalmic solution of any one of claims 5 to 8, wherein the tonicity agent is an ionic tonicity agent.

15 10. The ophthalmic solution of any one of claims 1 to 9 which is a multi-dose ophthalmic solution.

11. A method of providing preservative efficacy to an ophthalmic solution comprising epinastine or a salt thereof wherein the ophthalmic solution is substantially free of preservatives and ingredients with preservative efficacy, by composing epinastine or the salt thereof in a concentration of over 0.075% (w/v).
20

25 12. A method of maintaining preservative efficacy in an

ophthalmic solution comprising epinastine or a salt thereof wherein the ophthalmic solution is substantially free of preservatives and ingredients with preservative efficacy, by composing epinastine or the salt thereof in a
5 concentration of over 0.075% (w/v).