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(54) Title: OPHTHALMIC COMPOSITIONS COMPRISING COMBINATIONS OF A CARBONIC ANHYDRASE INHIBITOR AND A β -ADRENERGIC ANTAGONIST (57) Abstract Combinations of a β -adrenergic antagonist and a topical carbonic anhydrase inhibitor are particularly useful in the treatment of ocular hypertension, especially in patients insufficiently responsive to treatment with β -adrenergic antagonists.		

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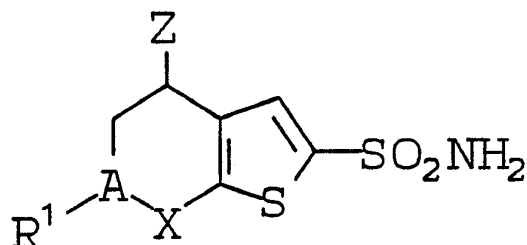
10 TITLE OF THE INVENTION

OPHTHALMIC COMPOSITIONS COMPRISING COMBINATIONS OF A
CARBONIC ANHYDRASE INHIBITOR AND A B-ADRENERGIC
ANTAGONIST

15 SUMMARY OF THE INVENTION

This invention relates to novel ophthalmic
compositions comprising a topical carbonic anhydrase
inhibitor of structure:

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wherein A, Z, R¹ and X are as hereinafter defined, or

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an ophthalmologically acceptable salt thereof and a
B-adrenergic antagonist selected from betaxolol,
buprenolol, carteolol, levobunolol, metipranolol, and
timolol, or an ophthalmologically acceptable salt
thereof.

The invention is also concerned with the use
of the novel ophthalmic compositions in the treatment
of ocular hypertension.

More particularly, it relates to such
ophthalmic combinations and their use in the
treatment of ocular hypertension and glaucoma,
wherein the B-adrenergic antagonist is 1-(~~tert~~-
butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-
3-yl)oxy]-2-propanol, or an ophthalmologically
acceptable salt thereof which name includes the
(S)-(-)- and (R)-(+)- enantiomers and any mixtures
thereof, including racemic material. The (S)-(-)-
enantiomer is generally known as timolol.

BACKGROUND OF THE INVENTION

Glaucoma is a degenerative disease of the
eye wherein the intraocular pressure is too high to
permit normal eye function. As a result, damage may
occur to the optic nerve head and result in
irreversible loss of visual function. If untreated,
glaucoma may eventually lead to blindness. Ocular
hypertension, i.e., the condition of elevated
intraocular pressure without optic nerve head damage
or characteristic glaucomatous visual field defects,
is now believed by the majority of ophthalmologists
to represent merely the earliest phase in the onset
of glaucoma.

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Many of the drugs formerly used to treat glaucoma proved not entirely satisfactory. The early methods of treatment of glaucoma employing pilocarpine produced undesirable local effects that
5 made this drug, though valuable, unsatisfactory as a first line drug. More recently, clinicians have noted that many β -adrenergic antagonists are effective in reducing intraocular pressure. While
10 many of these agents are effective for this purpose, there exist some patients with whom this treatment is not effective or not sufficiently effective. Many of these agents also have other characteristics, e.g., membrane stabilizing activity, that become more
15 apparent with increased doses and render them unacceptable for chronic ocular use.

The β -adrenergic antagonist (S)-1-(tert-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)-oxy]-2-propanol, timolol, was found to reduce
20 intraocular pressure and to be devoid of many unwanted side effects associated with pilocarpine and, in addition, to possess advantages over many other β -adrenergic antagonists, e.g., to be devoid of local anesthetic properties, to have a long duration
25 of activity, and to display minimal loss of effect with increased duration of dosing.

Although pilocarpine and β -adrenergic antagonists reduce intraocular pressure, none of these drugs manifests its action by inhibiting the
30 enzyme carbonic anhydrase, and thus they do not take advantage of reducing the contribution to aqueous humor formation made by the carbonic anhydrase pathway.

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Agents referred to as carbonic anhydrase inhibitors block or impede this inflow pathway by inhibiting the enzyme carbonic anhydrase. While such carbonic anhydrase inhibitors are now used to treat
5 intraocular pressure by systemic routes, they thereby have the distinct disadvantage of inhibiting carbonic anhydrase throughout the entire body. Such a gross disruption of a basic enzyme system is justified only during an acute attack of alarmingly elevated
10 intraocular pressure, or when no other agent is effective.

For several years, the desirability of directing the carbonic anhydrase inhibitor to only the desired ocular target tissue has been
15 recognized. Because carbonic anhydrase inhibitors have a profound effect in altering basic physiological processes, the avoidance of a systemic route of administration serves to diminish, if not entirely eliminate, those side effects caused by
20 inhibition of carbonic anhydrase such as metabolic acidosis, vomiting, numbness, tingling, general malaise and the like. Topically effective carbonic anhydrase inhibitors are disclosed in U.S. Patent Nos. 4,386,098; 4,416,890; 4,426,388; 4,668,697;
25 and 4,863,922 and PCT Publication WO 91/15486. As yet, no topically effective carbonic anhydrase inhibitors are generally available for clinical use.

Thus, when a carbonic anhydrase inhibitor is combined with a β -adrenergic antagonist, there is
30 experienced an effect that reduces the intraocular pressure below that obtained by either medicament individually.

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The activity of carbonic anhydrase inhibitors currently under development wanes 6 to 8 hours post-dose, meaning that as single agents these carbonic anhydrase inhibitors must be administered at least three times a day to maintain the desired lowering of intraocular pressure. The combination of this invention maintains the desired lowering of intraocular pressure for a full twelve hours. Because of this increased duration of action, the combination disclosed herein is effective when administered only twice a day. Patient compliance is anticipated to be greater with twice a day administration than with three times a day administration.

The use of oral carbonic anhydrase inhibitors in combination with the topical B-adrenergic antagonist timolol and the resulting multiplicity of their effects is disclosed in Berson et al., American Journal of Ophthalmology 1981, 92, 788-791. However, the combination of an oral carbonic anhydrase inhibitor with a topical B-adrenergic antagonist presents two disadvantages. The first disadvantage is that the systemic use of a carbonic anhydrase inhibitor inhibits carbonic anhydrase throughout the body and exerts the same profound negative effects on basic metabolism whether it is used alone or in combination with a topical B-adrenergic antagonist. Secondly, there is poor patient compliance with simultaneous administration of both an oral and topical medicament.

The combination disclosed herein is effective either by co-administration of the

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medicaments in one solution or as a combined therapy achieved by prior administration of either the carbonic anhydrase inhibitor or the β -adrenergic antagonist followed by administration of the other
5 solution. The use of a single solution containing both active medicaments is preferred.

The combination of this invention is suggested in U.S. Patent No. 4,863,922, but a precise
10 formulation of the relative combination of medicaments to give effective reduction of intraocular pressure is neither taught nor disclosed therein.

There exists a patient population
15 insufficiently responsive to available β -adrenergic antagonists who will benefit from the combination disclosed herein. Because of the combined effect of the β -adrenergic antagonist and the carbonic anhydrase inhibitor, these otherwise refractory
20 patients can obtain a marked beneficial reduction in intraocular pressure from such a combination.

Furthermore, there exists a patient
population who will benefit from a combination where the minimal dosage of one or both of the medicaments
25 is employed, thus minimizing the possibility of the occurrence of undesirable effects of one or both of the medicaments which would be more likely to become apparent with chronic use at the higher dosage.

30 DETAILED DESCRIPTION OF THE INVENTION

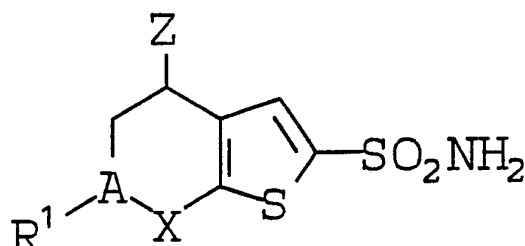
The novel ophthalmic compositions of this invention comprise a therapeutically effective amount of a topical carbonic anhydrase inhibitor and a

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B-adrenergic antagonist. The topical carbonic anhydrase inhibitor of the novel composition has the structural formula:

5

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or an ophthalmologically acceptable salt thereof wherein:

15 A is carbon or nitrogen, preferably carbon;

Z is -NHR or -OR;

R is C₁₋₆ alkyl, either straight or branched chain, preferably C₂₋₄ alkyl such as ethyl, propyl or isobutyl;

20 R¹ is

(a) hydrogen,

(b) C₁₋₃ alkyl, preferably methyl, ethyl or n-propyl, or

(c) C₁₋₄ alkoxy-C₁₋₄ alkyl, preferably methoxypropyl; and

25

X is -S(O)₂- or -C(O)₂-.

The carbon atoms to which Z and R¹ are bonded may be chiral. When named according to absolute configuration, e.g., (R,S) or (S,S), the first letter represents the chirality the carbon atom to which Z is bonded and the second letter represents the charality of A when A is carbon. The carbonic anhydrase inhibitors of this invention accordingly may be used as diastereomeric mixtures or single enantiomers or as racemic mixtures.

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The β -adrenergic antagonist of the novel composition is selected from betaxolol, bufenolol, carteolol, levobunolol, metipranolol, and timolol, or an ophthalmologically acceptable salt thereof.

5 Most of the β -adrenergic antagonists and carbonic anhydrase inhibitors recited above have at least one asymmetric carbon atom and accordingly may exist as diastereomers or (+)- or (-)-enantiomers. This invention contemplates the use of any of the
10 diastereomers or enantiomers or mixtures thereof including racemic forms.

The preferred β -adrenergic antagonist for use in the novel composition of this invention is timolol as its maleate salt.

15 The novel ophthalmic formulations of this invention comprise about 0.05 to 5% (w/w) of carbonic anhydrase inhibitor, usually about 0.5 to 3% (w/w) and about 0.01 to 1% (w/w) of β -adrenergic antagonist, preferably about 0.1 to 0.5% (w/w) to be
20 administered on a 1 to 2 times a day schedule.

The novel method of this invention comprises the topical ocular administration of about 0.025 to 5 mg per day, preferably about 0.25 to 3 mg per day, of carbonic anhydrase inhibitor and concomitant,
25 prior, or previous administration of about 0.005 to 1 mg per day, preferably about 0.05 to 0.5 mg per day, of β -adrenergic antagonist to each eye.

As a unit dosage, between 0.025 and 2.5 mg of the carbonic anhydrase inhibitor and 0.005 to
30 0.5 mg of the β -adrenergic antagonist are applied to the eye; preferably, 0.25 to 1.5 mg of the carbonic anhydrase inhibitor and 0.05 to 0.25 mg of the β -adrenergic antagonist.

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Suitable subjects for the administration of the formulation of the present invention include primates, man and other animals, particularly man and domesticated animals such as cats and dogs.

5 For topical ocular administration the novel formulations of this invention may take the form of solutions, gels, ointments, suspensions or solid inserts, formulated so that a unit dosage comprises a therapeutically effective amount of each active
10 component or some submultiple thereof.

Typical ophthalmologically acceptable carriers for the novel formulations are, for example, water, mixtures of water and water-miscible solvents such as lower alkanols or aralkanols, vegetable oils,
15 polyalkylene glycols, petroleum based jelly, ethyl cellulose, ethyl oleate, carboxymethylcellulose, polyvinylpyrrolidone, isopropyl myristate and other conventionally employed acceptable carriers. The pharmaceutical preparation may also contain non-toxic
20 auxiliary substances such as emulsifying, preserving, wetting agents, bodying agents and the like, as for example, polyethylene glycols 200, 300, 400 and 600, carbowaxes 1,000, 1,500, 4,000, 6,000 and
25 10,000, antibacterial components such as quaternary ammonium compounds, phenylmercuric salts known to have cold sterilizing properties and which are non-injurious in use, thimerosal, benzalkonium chloride, methyl and propyl paraben, benzyldodecinium
30 bromide, benzyl alcohol, phenylethanol, buffering ingredients such as sodium chloride, sodium borate, sodium acetate, or gluconate buffers, and other

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conventional ingredients such as sorbitan mono-
laurate, triethanolamine, polyoxyethylene sorbitan
monopalmitate, dioctyl sodium sulfosuccinate,
5 monothioglycerol, thiosorbitol, ethylenediamine tetra-
acetic acid, and the like. Additionally, suitable
ophthalmic vehicles can be used as carrier media for
the present purpose including conventional phosphate
buffer vehicle systems, isotonic boric acid vehicles,
isotonic sodium chloride vehicles, isotonic sodium
10 borate vehicles and the like.

The formulation may also include a gum such
as gellan gum at a concentration of 0.1% to 2% by
weight so that the aqueous eyedrops gel on contact
with the eye, thus providing the advantages of a
15 solid ophthalmic insert as described in U.S. Patent
4,861,760.

The pharmaceutical preparation may also be
in the form of a solid insert such as one which after
dispensing the drug remains essentially intact as
20 described in U.S. Patents 4,256,108; 4,160,452; and
4,265,874; or a bio-erodible insert that either is
soluble in lacrimal fluids, or otherwise disintegrates
as described in U.S. Patent 4,287,175 or EPO
publication 0,077,261.
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The following examples of ophthalmic formulations are given by way of illustration.

EXAMPLE 1

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<u>SOLUTION COMPOSITION</u>	<u>I</u>	<u>II</u>	<u>III</u>
(S,S)-(-)-5,6-dihydro-4-ethyl- amino-6-methyl-4H-thieno- [2,3b]thiopyran-2-sulfonamide- 7,7-dioxide monohydrochloride	22.26 g	22.26 g	1.113 g
(S)-(-)-1-(tert -butylamino)- 3-[(4-morpholino-1,2,5- thiadiazol-3-yl)oxy]-2- propanol maleate	6.834 g	1.367 g	6.834 g
Sodium citrate.2H ₂ O	2.940 g	2.940 g	2.940 g
Benzalkonium Chloride	0.075 g	0.075 g	0.075 g
Hydroxyethylcellulose	5.00 g	5.00 g	5.00 g
Sodium hydroxide q.s.	pH = 6.0	pH = 6.0	pH = 6.0
Mannitol	16.00 g	21.00 g	35.90 g
Water for injection q.s. ad.	1000 g	1000 g	1000 g

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The active compounds, sodium citrate, benzalkonium chloride (in a 50% W/W solution), and mannitol are dissolved in approximately 400 mL water for injection in a tared and sterile vessel. The pH of the composition is adjusted to 6.0 by addition of 0.2 N sodium hydroxide solution, and water for injection is added until the weight of composition equals 750 g. The composition is sterilized by filtration, pushing the solution with a 2 bar pressure of 0.45 micron filtrated nitrogen. Then 250 g of a 2% hydroxyethylcellulose autoclaved solution is added and the obtained solution is homogenized by stirring with a magnetic stirring bar. The solution is aseptically subdivided into 3.5 mL aliquots and sealed.

EXAMPLE 2

<u>SOLUTION COMPOSITION</u>	<u>I</u>	<u>II</u>	<u>III</u>
(S,S)-(-)-5,6-dihydro-4-ethyl-amino-6-methyl-4H-thieno-[2,3b]thiopyran-2-sulfonamide-7,7-dioxide	1.0 mg	1.5 mg	0.5 mg
4-[2-hydroxy-3-(1-methylethyl)-amino]-propoxy]-2,3,6-trimethylphenol-1-acetate	0.3 mg	0.2 mg	0.4 mg
Monobasic sodium phosphate 2H ₂ O	Quantity sufficient to give final pH 5.5 - 6.0		
Dibasic sodium phosphate .12H ₂ O			

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	Benzalkonium chloride	0.10 mg	0.10 mg	0.10 mg
5	Polysorbate 80	0.2 mg	0.2 mg	0.2 mg
	Water for injection q.s. ad.	1.0 mL	1.0 mL	1.0 mL

10 The active compounds, phosphate buffer salts, benzalkonium chloride, and Polysorbate 80 are added to and suspended or dissolved in water. The pH of the composition is adjusted to 5.5-6.0 and diluted to volume. The composition is rendered sterile by filtration through a sterilizing filter.

15

EXAMPLE 3

	<u>SOLUTION COMPOSITION</u>	<u>I</u>	<u>II</u>
20	trans-5,6-dihydro-4-ethylamino-6-methyl-4H-thieno[2,3b]thiopyran-2-sulfonamide-7,7-dioxide	1.7 mg	0.8 mg
25	1-[4-[2-(cyclopropylmethoxy)-ethyl]phenoxy]-3-(1-methylethyl)-amino]-2-propanol	0.3 mg	0.2 mg
	Monobasic sodium phosphate.2H ₂ O	9.5 mg	9.5 mg
	Dibasic sodium phosphate.12H ₂ O	28.5 mg	28.5 mg
30	Benzalkonium chloride	0.10 mg	0.10 mg
	Sodium hydroxide q.s.	pH 6.0	pH 6.0
	Water for injection q.s. ad.	1.0 mL	1.0 mL

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The active compounds, phosphate buffer salts, and benzalkonium chloride are added to and dissolved in water. The pH of the composition is adjusted to 6.0 with sodium hydroxide and the final solution is diluted to volume. The solution is rendered sterile by filtration through a sterilizing filter.

10

EXAMPLE 4

<u>SOLUTION COMPOSITION</u>	<u>I</u>	<u>II</u>	<u>III</u>
(S,S)-(-)-5,6-dihydro-4-propyl-amino-6-methoxypropyl-4H-thieno-[2,3b]thiopyran-2-sulfonamide-7,7-dioxide monohydrochloride	21.0 g	21.0 g	1.5 g
(S)-(-)-1-(tert -butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate	6.8 g	1.3 g	6.8 g
Sodium citrate.2H ₂ O	2.9 g	2.9 g	2.9 g
Benzalkonium Chloride	0.075 g	0.075 g	0.075 g
Hydroxyethylcellulose	5.0 g	5.0 g	5.0 g
Sodium hydroxide q.s.	pH = 6.0	pH = 6.0	pH = 6.0
Mannitol	35.9 g	35.9 g	35.9 g
Water for injection q.s. ad.	1000 g	1000 g	1000 g

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The active compounds, sodium citrate, benzalkonium chloride (in a 50% W/W solution), and mannitol are dissolved in approximately 400 mL water for injection in a tared and sterile vessel. The pH of the composition is adjusted to 6.0 by addition of 0.2 N sodium hydroxide solution and water for injection is added until the weight of composition equals 750 g. The composition is sterilized by filtration, pushing the solution with a 2 bar pressure of 0.45 micron filtrated nitrogen. Then 250 g of a 2% hydroxyethylcellulose autoclaved solution is added and the obtained solution is homogenized by stirring with a magnetic stirring bar. The solution is aseptically subdivided into 3.5 mL aliquots and sealed.

EXAMPLE 5

20

<u>SOLUTION COMPOSITION</u>	<u>I</u>	<u>II</u>	<u>III</u>
(S,S)-(-)-5,6-dihydro-4-propylamino-6-methoxypropyl-4H-thieno[2,3b]thiopyran-2-sulfonamide-7,7-dioxide	1.0 mg	1.5 mg	0.5 mg
4-[2-hydroxy-3-(1-methylethyl)-amino]propoxy]-2,3,6-trimethylphenol-1-acetate	0.3 mg	0.2 mg	0.4 mg

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5	Monobasic sodium phosphate .2H ₂ O	Quantity sufficient to give		
	Dibasic sodium phosphate .12H ₂ O	final pH 5.5 - 6.0		
	Benzalkonium chloride	0.10 mg	0.10 mg	0.10 mg
	Polysorbate 80	0.2 mg	0.2 mg	0.2 mg
10	Water for injection q.s. ad.	1.0 mL	1.0 mL	1.0 mL

15 The active compounds, phosphate buffer salts, benzalkonium chloride, and Polysorbate 80 are added to and suspended or dissolved in water. The pH of the composition is adjusted to 5.5-6.0 and diluted to volume. The composition is rendered sterile by filtration through a sterilizing filter.

20

EXAMPLE 6

<u>SOLUTION COMPOSITION</u>		<u>I</u>	<u>II</u>
25	trans-5,6-dihydro-4-propylamino-6-methoxypropyl-4H-thieno[2,3b]thiopyran-2-sulfonamide-7,7-dioxide	1.7 mg	0.8 mg
	1-[4-[2-(cyclopropylmethoxy)ethyl]-phenoxy]-3-(1-methylethyl)amino]-2-propanol	0.3 mg	0.2 mg
30	Monobasic sodium phosphate.2H ₂ O	9.5 mg	9.5 mg

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	Dibasic sodium phosphate.12H ₂ O	28.5 mg	28.5 mg
5	Benzalkonium chloride	0.10 mg	0.10 mg
	Sodium hydroxide q.s.	pH 6.0	pH 6.0
	Water for injection q.s. ad.	1.0 mL	1.0 mL

10 The active compounds, phosphate buffer salts, and benzalkonium chloride are added to and dissolved in water. The pH of the composition is adjusted to 6.0 with sodium hydroxide and the final solution is diluted to volume. The solution is rendered sterile by filtration through a sterilizing filter.

EXAMPLE 7

20	<u>SOLUTION COMPOSITION</u>	<u>I</u>	<u>II</u>	<u>III</u>
	(S)-(+)-5,6-dihydro-4-isobutyl-amino-4H-thieno[2,3b]thiopyran-2-sulfonamide-7,7-dioxide mono-hydrochloride	21.0 g	21.0 g	1.5 g
25				
	(S)-(-)-1-(tert-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate	6.8 g	1.3 g	6.8 g
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	Sodium citrate.2H ₂ O	2.9 g	2.9 g	2.9 g
5	Benzalkonium Chloride	0.075 g	0.075 g	0.075 g
	Hydroxyethylcellulose	5.0 g	5.0 g	5.0 g
	Sodium hydroxide q.s.	pH = 6.0	pH = 6.0	pH = 6.0
10	Mannitol	35.9 g	35.9 g	35.9 g
	Water for injection q.s. ad.	1000 g	1000 g	1000 g

15 The active compounds, sodium citrate,
benzalkonium chloride (in a 50% W/W solution), and
mannitol are dissolved in approximately 400 mL water
for injection in a tared and sterile vessel. The pH
of the composition is adjusted to 6.0 by addition of
0.2 N sodium hydroxide solution and water for
20 injection is added until the weight of composition
equals 750 g. The composition is sterilized by
filtration, pushing the solution with a 2 bar
pressure of 0.45 micron filtrated nitrogen. Then 250
g of a 2% hydroxyethylcellulose autoclaved solution
25 is added and the obtained solution is homogenized by
stirring with a magnetic stirring bar. The solution
is aseptically subdivided into 3.5 mL aliquots and
sealed.

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EXAMPLE 8

<u>SOLUTION COMPOSITION</u>		<u>I</u>	<u>II</u>	<u>III</u>
5	(S)-(+)-5,6-dihydro-4-isobutyl- amino-4H-thieno[2,3b]thiopyran- 2-sulfonamide-7,7-dioxide	1.0 mg	1.5 mg	0.5 mg
10	4-[2-hydroxy-3-(1-methylethyl)- amino]propoxy]-2,3,6- trimethylphenol-1-acetate	0.3 mg	0.2 mg	0.4 mg
15	Monobasic sodium phosphate .2H ₂ O Dibasic sodium phosphate .12H ₂ O	Quantity sufficient to give final pH 5.5 - 6.0		
	Benzalkonium chloride	0.10 mg	0.10 mg	0.10 mg
20	Polysorbate 80	0.2 mg	0.2 mg	0.2 mg
	Water for injection q.s. ad.	1.0 mL	1.0 mL	1.0 mL

25 The active compounds, phosphate buffer
salts, benzalkonium chloride, and Polysorbate 80 are
added to and suspended or dissolved in water. The pH
of the composition is adjusted to 5.5-6.0 and diluted
to volume. The composition is rendered sterile by
30 filtration through a sterilizing filter.

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EXAMPLE 9

<u>SOLUTION COMPOSITION</u>		<u>I</u>	<u>II</u>
5	(S)-(+)-5,6-dihydro-4-isobutyl- amino-4H-thieno[2,3b]thiopyran- 2-sulfonamide-7,7-dioxide	1.7 mg	0.8 mg
10	1-[4-[2-(cyclopropylmethoxy)- ethyl]-phenoxy]-3-(1-methylethyl)- amino]-2-propanol	0.3 mg	0.2 mg
	Monobasic sodium phosphate.2H ₂ O	9.5 mg	9.5 mg
15	Dibasic sodium phosphate.12H ₂ O	28.5 mg	28.5 mg
	Benzalkonium chloride	0.10 mg.	0.10 mg
	Sodium hydroxide q.s.	pH 6.0	pH 6.0
20	Water for injection q.s. ad.	1.0 mL	1.0 mL

25 The active compounds, phosphate buffer salts, and benzalkonium chloride are added to and dissolved in water. The pH of the composition is adjusted to 6.0 with sodium hydroxide and the final solution is diluted to volume. The solution is rendered sterile by filtration through a sterilizing filter.

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EXAMPLE 10

<u>SOLUTION COMPOSITION</u>		<u>I</u>	<u>II</u>
5	(S,S)-(-)-5,6-dihydro-4-ethyl-amino-6-methyl-4H-thieno[2,3b]-thiopyran-2-sulfonamide-7,7-dioxide monohydrochloride	2.0 mg	0.2 mg
10	(S)-(-)-1-(tert -butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate	0.5 mg	0.5 mg
15	GELRITE™ gellan gum	6.0 mg	6.0 mg
	Monobasic sodium phosphate .2H ₂ O	Quantity sufficient to give final pH 5.5 - 6.0	
	Dibasic sodium phosphate .12H ₂ O		
20			
	Benzylododecinium bromide	0.10 mg	0.10 mg
	Polysorbate 80	0.2 mg	0.2 mg
25	Water for injection q.s. ad.	1.0 mL	1.0 mL

30 The active compounds, GELRITE™ gellan gum, phosphate buffer salts, benzylododecinium bromide and Polysorbate 80 are added to and suspended or dissolved in water. The pH of the composition is adjusted to 5.5-6.0 and diluted to volume. The composition is rendered sterile by ionizing radiation.

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EXAMPLE 11

<u>SOLUTION COMPOSITION</u>		<u>I</u>	<u>II</u>
5	(S)-(+)-5,6-dihydro-4-isobutyl- amino-4H-thieno[2,3b]thiopyran- 2-sulfonamide-7,7-dioxide	3.0 mg	0.5 mg
10	(S)-(-)-1-(tert -butylamino)- 3-[(4-morpholino-1,2,5- thiadiazol-3-yl)oxy]-2- propanol maleate	0.5 mg	0.5 mg
	GELRITE™ gellan gum	6.0 mg	6.0 mg
15	Monobasic sodium phosphate .2H ₂ O Dibasic sodium phosphate .12H ₂ O	Quantity sufficient to give final pH 5.0 - 6.0	
20	Benzylododecinium bromide	0.10 mg	0.10 mg
	Polysorbate 80	0.2 mg	0.2 mg
25	Water for injection q.s. ad.	1.0 mL	1.0 mL

30 The active compounds, GELRITE™ gellan gum,
 phosphate buffer salts, benzylododecinium bromide and
 Polysorbate 80 are added to and suspended or
 dissolved in water. The pH of the composition is
 adjusted to 5.0-6.0 and diluted to volume. The
 composition is rendered sterile by ionizing radiation.

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EXAMPLE 12

<u>SOLUTION COMPOSITION</u>		<u>I</u>	<u>II</u>
5	(S,S)-(-)-5,6-dihydro-4-propyl-amino-6-methoxypropyl-4H-thieno[2,3b]thiopyran-2-sulfonamide-7,7-dioxide	2.0 mg	0.2 mg
10	(S)-(-)-1-(<u>tert</u> -butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate	0.5 mg	0.5 mg
15	GELRITE™ gellan gum	6.0 mg	6.0 mg
	Monobasic sodium phosphate .2H ₂ O	Quantity sufficient to give final pH 5.5 - 6.0	
	Dibasic sodium phosphate .12H ₂ O		
20			
	Benzylododecinium bromide	0.10 mg	0.10 mg
	Polysorbate 80	0.2 mg	0.2 mg
25	Water for injection q.s. ad.	1.0 mL	1.0 mL

30 The active compounds, GELRITE™ gellan gum, phosphate buffer salts, benzylododecinium bromide and Polysorbate 80 are added to and suspended or dissolved in water. The pH of the composition is adjusted to 5.5-6.0 and diluted to volume. The composition is rendered sterile by ionizing radiation.

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EXAMPLE 13

<u>SOLUTION COMPOSITION</u>		<u>I</u>	<u>II</u>
5	(R)-(-)-5,6-dihydro-4-iso-butylamino-4H-thieno[2,3b]-thio-pyran-2-sulfonamide-7,7-dioxide	2.0 mg	0.5 mg
10	4-[2-hydroxy-3-(1-methylethyl)-amino]propoxy]-2,3,6-trimethylphenol-1-acetate	0.5 mg	0.5 mg
	GELRITE™ gellan gum	6.0 mg	6.0 mg
15	Monobasic sodium phosphate .2H ₂ O	Quantity sufficient to give final pH 5.5 - 6.0	
	Dibasic sodium phosphate .12H ₂ O		
20	Benzyldodecinium bromide	0.10 mg	0.10 mg
	Polysorbate 80	0.2 mg	0.2 mg
	Water for injection q.s. ad.	1.0 mL	1.0 mL
25	The active compounds, GELRITE™ gellan gum, phosphate buffer salts, benzyldodecinium bromide and Polysorbate 80 are added to and suspended or dissolved in water. The pH of the composition is adjusted to 5.5-6.0 and diluted to volume. The composition is rendered sterile by ionizing radiation.		
30			

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EXAMPLE 14

<u>SOLUTION COMPOSITION</u>		<u>I</u>	<u>II</u>
5	cis-5,6-dihydro-4-ethylamino- 6-methyl-4H-thieno[2,3b]thiopyran- 2-sulfonamide-7,7-dioxide monohydrochloride	2.0 mg	0.2 mg
10	4-[2-hydroxy-3-(1-methylethyl)- amino]propoxy]-2,3,6- trimethylphenol-1-acetate	0.5 mg	0.5 mg
	GELRITE™ gellan gum	6.0 mg	6.0 mg
15	Monobasic sodium phosphate .2H ₂ O	Quantity sufficient to give final pH 5.5 - 6.0	
	Dibasic sodium phosphate .12H ₂ O		
20	Benzyldodecinium bromide	0.10 mg	0.10 mg
	Polysorbate 80	0.2 mg	0.2 mg
25	Water for injection q.s. ad.	1.0 mL	1.0 mL

30 The active compounds, GELRITE™ gellan gum, phosphate buffer salts, benzyldodecinium bromide and Polysorbate 80 are added to and suspended or dissolved in water. The pH of the composition is adjusted to 5.5-6.0 and diluted to volume. The composition is rendered sterile by ionizing radiation.

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EXAMPLE 15

<u>SOLUTION COMPOSITION</u>		<u>I</u>	<u>II</u>
5	cis-5,6-dihydro-4-propyl- amino-6-methoxypropyl-4H- thieno[2,3b]thiopyran-2- sulfonamide-7,7-dioxide	2.0 mg	0.5 mg
10	4-[2-hydroxy-3-(1-methylethyl)- amino]propoxy]-2,3,6- trimethylphenol-1-acetate	0.5 mg	0.5 mg
	GELRITE™ gellan gum	6.0 mg	6.0 mg
15	Monobasic sodium phosphate .2H ₂ O Dibasic sodium phosphate .12H ₂ O	Quantity sufficient to give final pH 5.5 - 6.0	
20	Benzyldodecinium bromide	0.10 mg	0.10 mg
	Polysorbate 80	0.2 mg	0.2 mg
25	Water for injection q.s. ad.	1.0 mL	1.0 mL

25 The active compounds, GELRITE™ gellan gum,
phosphate buffer salts, benzyldodecinium bromide and
Polysorbate 80 are added to and suspended or
30 dissolved in water. The pH of the composition is
adjusted to 5.5-6.0 and diluted to volume. The
composition is rendered sterile by ionizing radiation.

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EXAMPLE 16

<u>SOLUTION COMPOSITION</u>		<u>I</u>	<u>II</u>
5	5,6-dihydro-4-ethylamino- 6-methyl-4H-thieno[2,3b]thiopyran- 2-sulfonamide-7,7-dioxide monohydrochloride	2.0 mg	0.2 mg
10	1-[4-[2-(cyclopropylmethoxy)ethyl]- phenoxy]-3-(1-methylethyl)amino]- 2-propanol	0.5 mg	0.5 mg
	GELRITE™ gellan gum	6.0 mg	6.0 mg
15	Monobasic sodium phosphate .2H ₂ O	Quantity sufficient to give final pH 5.5 - 6.0	
	Dibasic sodium phosphate .12H ₂ O		
20	Benzylododecinium bromide	0.10 mg	0.10 mg
	Polysorbate 80	0.2 mg	0.2 mg
25	Water for injection q.s. ad.	1.0 mL	1.0 mL

The active compounds, GELRITE™ gellan gum, phosphate buffer salts, benzylododecinium bromide and Polysorbate 80 are added to and suspended or dissolved in water. The pH of the composition is adjusted to 5.5-6.0 and diluted to volume. The composition is rendered sterile by ionizing radiation.

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EXAMPLE 17

<u>SOLUTION COMPOSITION</u>		<u>I</u>	<u>II</u>
5	5,6-dihydro-4-isobutylamino- 4H-thieno[2,3b]thiopyran- 2-sulfonamide-7,7-dioxide	2.0 mg	0.5 mg
10	1-[4-[2-(cyclopropylmethoxy)ethyl]- phenoxy]-3-(1-methylethyl)amino]- 2-propanol	0.5 mg	0.5 mg
	GELRITE™ gellan gum	6.0 mg	6.0 mg
15	Monobasic sodium phosphate .2H ₂ O	Quantity sufficient to give final pH 5.5 - 6.0	
	Dibasic sodium phosphate .12H ₂ O		
20	Benzyldodecinium bromide	0.10 mg	0.10 mg
	Polysorbate 80	0.2 mg	0.2 mg
	Water for injection q.s. ad.	1.0 mL	1.0 mL
25	The active compounds, GELRITE™ gellan gum, phosphate buffer salts, benzyldodecinium bromide and Polysorbate 80 are added to and suspended or dissolved in water. The pH of the composition is adjusted to 5.5-6.0 and diluted to volume. The		
30			
	composition is rendered sterile by ionizing radiation.		

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EXAMPLE 18

<u>SOLUTION COMPOSITION</u>		<u>I</u>	<u>II</u>
5	5,6-dihydro-4-propylamino- 6-methoxypropyl-4H- thieno[2,3b]thiopyran-2- sulfonamide-7,7-dioxide	2.0 mg	0.2 mg
10	1-[4-[2-(cyclopropylmethoxy)ethyl]- phenoxy]-3-(1-methylethyl)amino]- 2-propanol	0.5 mg	0.5 mg
	GELRITE™ gellan gum	6.0 mg	6.0 mg
15	Monobasic sodium phosphate .2H ₂ O	Quantity sufficient to give final pH 5.5 - 6.0	
	Dibasic sodium phosphate .12H ₂ O		
20	Benzyldodecinium bromide	0.10 mg	0.10 mg
	Polysorbate 80	0.2 mg	0.2 mg
25	Water for injection q.s. ad.	1.0 mL	1.0 mL

30 The active compounds, GELRITE™ gellan gum,
 phosphate buffer salts, benzyldodecinium bromide and
 Polysorbate 80 are added to and suspended or
 dissolved in water. The pH of the composition is
 adjusted to 5.5-6.0 and diluted to volume. The
 composition is rendered sterile by ionizing radiation.

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EXAMPLE 19

<u>SOLUTION COMPOSITION</u>		<u>I</u>	<u>II</u>	<u>III</u>
5	3,4-Dihydro-4-methoxy-2-methyl- 2H-thieno[3,2-e]-1,2-thiazine- 6-sulfonamide-1,1-dioxide	22.26 g	22.26 g	1.113 g
10	(S)-(-)-1-(<u>tert</u> -butylamino)- 3-[(4-morpholino-1,2,5- thiadiazol-3-yl)oxy]-2- propanol maleate	6.834 g	1.367 g	6.834 g
15	Sodium citrate.2H ₂ O	2.940 g	2.940 g	2.940 g
	Benzalkonium Chloride	0.075 g	0.075 g	0.075 g
20	Hydroxyethylcellulose	5.00 g	5.00 g	5.00 g
	Sodium hydroxide q.s.	pH = 6.0	pH = 6.0	pH = 6.0
	Mannitol	16.00 g	21.00 g	35.90 g
25	Water for injection q.s. ad.	1000 g	1000 g	1000 g

30

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EXAMPLE 20

5	<u>SOLUTION COMPOSITION</u>	I	II	III
	3,4-Dihydro-4-ethylamino-2-methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride	22.26 g	22.26 g	1.113 g
10	(S)-(-)-1-(tert -butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate	6.834 g	1.367 g	6.834 g
15	Sodium citrate.2H ₂ O	2.940 g	2.940 g	2.940 g
	Benzalkonium Chloride	0.075 g	0.075 g	0.075 g
20	Hydroxyethylcellulose	5.00 g	5.00 g	5.00 g
	Sodium hydroxide q.s.	pH = 6.0	pH = 6.0	pH = 6.0
	Mannitol	16.00 g	21.00 g	35.90 g
25	Water for injection q.s. ad.	1000 g	1000 g	1000 g

30

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EXAMPLE 21

5	<u>SOLUTION COMPOSITION</u>	<u>I</u>	<u>II</u>	<u>III</u>
	3,4-Dihydro-2-methyl-4-(2-methyl)propylamino-2H-thieno-[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride	22.26 g	22.26 g	1.113 g
10	(S)-(-)-1-(tert-butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate	6.834 g	1.367 g	6.834 g
15	Sodium citrate.2H ₂ O	2.940 g	2.940 g	2.940 g
	Benzalkonium Chloride	0.075 g	0.075 g	0.075 g
20	Hydroxyethylcellulose	5.00 g	5.00 g	5.00 g
	Sodium hydroxide q.s.	pH = 6.0	pH = 6.0	pH = 6.0
	Mannitol	16.00 g	21.00 g	35.90 g
25	Water for injection q.s. ad.	1000 g	1000 g	1000 g

30

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EXAMPLE 22

<u>SOLUTION COMPOSITION</u>		<u>I</u>	<u>II</u>	<u>III</u>
5	R-(+)-3,4-Dihydro-4-ethylamino- 2-methyl)-2H-thieno[3,2-e]-1,2- thiazine-6-sulfonamide-1,1- dioxide hydrochloride	22.26 g	22.26 g	1.113 g
10	(S)-(-)-1-(tert -butylamino)- 3-[(4-morpholino-1,2,5- thiadiazol-3-yl)oxy]-2- propanol maleate	6.834 g	1.367 g	6.834 g
15	Sodium citrate.2H ₂ O	2.940 g	2.940 g	2.940 g
	Benzalkonium Chloride	0.075 g	0.075 g	0.075 g
20	Hydroxyethylcellulose	5.00 g	5.00 g	5.00 g
	Sodium hydroxide q.s.	pH = 6.0	pH = 6.0	pH = 6.0
	Mannitol	16.00 g	21.00 g	35.90 g
25	Water for injection q.s. ad.	1000 g	1000 g	1000 g

30

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EXAMPLE 23

<u>SOLUTION COMPOSITION</u>		<u>I</u>	<u>II</u>	<u>III</u>
5	R-(+)-3,4-Dihydro-4-ethylamino- 2-(2-methoxy)ethyl-2H-thieno- [3,2-e]-1,2-thiazine-6-sulfon- amide-1,1-dioxide hydrochloride	22.26 g	22.26 g	1.113 g
10	(S)-(-)-1-(tert -butylamino)- 3-[(4-morpholino-1,2,5- thiadiazol-3-yl)oxy]-2- propanol maleate	6.834 g	1.367 g	6.834 g
15	Sodium citrate.2H ₂ O	2.940 g	2.940 g	2.940 g
	Benzalkonium Chloride	0.075 g	0.075 g	0.075 g
20	Hydroxyethylcellulose	5.00 g	5.00 g	5.00 g
	Sodium hydroxide q.s.	pH = 6.0	pH = 6.0	pH = 6.0
	Mannitol	16.00 g	21.00 g	35.90 g
25	Water for injection q.s. ad.	1000 g	1000 g	1000 g

30

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EXAMPLE 24

5	<u>SOLUTION COMPOSITION</u>	<u>I</u>	<u>II</u>	<u>III</u>
	R-(+)-3,4-Dihydro-2-(2-methoxy)- ethyl-4-propylamino-2H-thieno- [3,2-e]-1,2-thiazine-6-sulfon- amide-1,1-dioxide hydrochloride	22.26 g	22.26 g	1.113 g
10	(S)-(-)-1-(tert-butylamino)- 3-[(4-morpholino-1,2,5- thiadiazol-3-yl)oxy]-2- propanol maleate	6.834 g	1.367 g	6.834 g
15	Sodium citrate.2H ₂ O	2.940 g	2.940 g	2.940 g
	Benzalkonium Chloride	0.075 g	0.075 g	0.075 g
20	Hydroxyethylcellulose	5.00 g	5.00 g	5.00 g
	Sodium hydroxide q.s.	pH = 6.0	pH = 6.0	pH = 6.0
	Mannitol	16.00 g	21.00 g	35.90 g
25	Water for injection q.s. ad.	1000 g	1000 g	1000 g

30

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EXAMPLE 25

<u>SOLUTION COMPOSITION</u>		<u>I</u>	<u>II</u>
5	3,4-Dihydro-4-methoxy-2-methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide	2.0 mg	0.2 mg
10	(S)-(-)-1-(tert -butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate	0.5 mg	0.5 mg
15	GELRITE™ gellan gum	6.0 mg	6.0 mg
	Monobasic sodium phosphate .2H ₂ O	Quantity sufficient to give final pH 5.5 - 6.0	
	Dibasic sodium phosphate .12H ₂ O		
20			
	Benzyldodecinium bromide	0.10 mg	0.10 mg
	Polysorbate 80	0.2 mg	0.2 mg
25	Water for injection q.s. ad.	1.0 mL	1.0 mL

The active compounds, GELRITE™ gellan gum, phosphate buffer salts, benzyldodecinium bromide and Polysorbate 80 are added to and suspended or dissolved in water. The pH of the composition is adjusted to 5.5-6.0 and diluted to volume. The composition is rendered sterile by ionizing radiation.

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EXAMPLE 26

5	<u>SOLUTION COMPOSITION</u>	<u>I</u>	<u>II</u>
	3,4-Dihydro-4-ethylamino-2-methyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride	2.0 mg	0.2 mg
10	(S)-(-)-1-(tert -butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate	0.5 mg	0.5 mg
15	GELRITE™ gellan gum	6.0 mg	6.0 mg
	Monobasic sodium phosphate .2H ₂ O	Quantity sufficient to give final pH 5.5 - 6.0	
20	Dibasic sodium phosphate .12H ₂ O		
	Benzyldodecinium bromide	0.10 mg	0.10 mg
25	Polysorbate 80	0.2 mg	0.2 mg
	Water for injection q.s. ad.	1.0 mL	1.0 mL

The active compounds, GELRITE™ gellan gum, phosphate buffer salts, benzyldodecinium bromide and Polysorbate 80 are added to and suspended or dissolved in water. The pH of the composition is adjusted to 5.5-6.0 and diluted to volume. The composition is rendered sterile by ionizing radiation.

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EXAMPLE 27

	<u>SOLUTION COMPOSITION</u>	<u>I</u>	<u>II</u>
5	3,4-Dihydro-2-methy-4-(2-methyl)propylamino-2H-thieno-[3,2-e]-1,2-thiazine-6-sulfonamide-1,1-dioxide hydrochloride		
10	(S)-(-)-1-(tert -butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate	2.0 mg	0.2 mg
15	GELRITE™ gellan gum	0.5 mg	0.5 mg
20	Monobasic sodium phosphate .2H ₂ O Dibasic sodium phosphate .12H ₂ O	Quantity sufficient to give final pH 5.5 - 6.0	
25	Benzyldodecinium bromide	0.10 mg	0.10 mg
	Polysorbate 80	0.2 mg	0.2 mg
30	Water for injection q.s. ad. 1.0 mL 1.0 mL The active compounds, GELRITE™ gellan gum, phosphate buffer salts, benzyldodecinium bromide and Polysorbate 80 are added to and suspended or dissolved in water. The pH of the composition is adjusted to 5.5-6.0 and diluted to volume. The composition is rendered sterile by ionizing radiation.		

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EXAMPLE 28

	<u>SOLUTION COMPOSITION</u>	<u>I</u>	<u>II</u>
5	R-(+)-3,4-Dihydro-4-ethyl- amino-2-methyl-2H-thieno- [3,2-e]-1,2-thiazine-6-sulfon- amide-1,1-dioxide hydrochloride	2.0 mg	0.2 mg
10	(S)-(-)-1-(tert -butylamino)- 3-[(4-morpholino-1,2,5- thiadiazol-3-yl)oxy]-2- propanol maleate	0.5 mg	0.5 mg
15	GELRITE™ gellan gum	6.0 mg	6.0 mg
20	Monobasic sodium phosphate .2H ₂ O Dibasic sodium phosphate .12H ₂ O	Quantity sufficient to give final pH 5.5 - 6.0	
25	Benzyldodecinium bromide	0.10 mg	0.10 mg
25	Polysorbate 80	0.2 mg	0.2 mg
	Water for injection q.s. ad.	1.0 mL	1.0 mL

The active compounds, GELRITE™ gellan gum,
 phosphate buffer salts, benzyldodecinium bromide and
 Polysorbate 80 are added to and suspended or dissolved in
 water. The pH of the composition is adjusted to 5.5-6.0 and
 diluted to volume. The composition is rendered sterile by
 ionizing radiation.

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EXAMPLE 29

<u>SOLUTION COMPOSITION</u>		<u>I</u>	<u>II</u>
5	R-(+)-3,4-Dihydro-4-ethyl-amino-2-(2-methoxy)ethyl-2H-thieno[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride	2.0 mg	0.2 mg
10	(S)-(-)-1-(<u>tert</u> -butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate	0.5 mg	0.5 mg
15	GELRITE™ gellan gum	6.0 mg	6.0 mg
	Monobasic sodium phosphate .2H ₂ O	Quantity sufficient to give final pH 5.5 - 6.0	
20	Dibasic sodium phosphate .12H ₂ O		
	Benzyldodecinium bromide	0.10 mg	0.10 mg
25	Polysorbate 80	0.2 mg	0.2 mg
	Water for injection q.s. ad.	1.0 mL	1.0 mL

30 The active compounds, GELRITE™ gellan gum, phosphate buffer salts, benzyldodecinium bromide and Polysorbate 80 are added to and suspended or dissolved in water. The pH of the composition is adjusted to 5.5-6.0 and diluted to volume. The composition is rendered sterile by ionizing radiation.

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EXAMPLE 30

	<u>SOLUTION COMPOSITION</u>	<u>I</u>	<u>II</u>
5	R-(+)-3,4-Dihydro-2-(2-methoxy)-ethyl-4-propylamino-2H-thieno-[3,2-e]-1,2-thiazine-6-sulfonamide 1,1-dioxide hydrochloride-	2.0 mg	0.2 mg
10	(S)-(-)-1-(tert -butylamino)-3-[(4-morpholino-1,2,5-thiadiazol-3-yl)oxy]-2-propanol maleate	0.5 mg	0.5 mg
15	GELRITE™ gellan gum	6.0 mg	6.0 mg
20	Monobasic sodium phosphate .2H ₂ O Dibasic sodium phosphate .12H ₂ O	Quantity sufficient to give final pH 5.5 - 6.0	
25	Benzyldodecinium bromide	0.10 mg	0.10 mg
	Polysorbate 80	0.2 mg	0.2 mg
	Water for injection q.s. ad.	1.0 mL	1.0 mL

30

The active compounds, GELRITE™ gellan gum, phosphate buffer salts, benzyldodecinium bromide and Polysorbate 80 are added to and suspended or dissolved in water. The pH of the composition is adjusted to 5.5-6.0 and diluted to volume. The composition is rendered sterile by ionizing radiation.

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EXAMPLE 31

<u>SOLUTION COMPOSITION</u>		<u>I</u>	<u>II</u>	<u>III</u>
5	(S,S)-(-)-5,6-dihydro-4-ethyl- amino-6-propyl-4H-thieno- [2,3b]thiopyran-2-sulfonamide- 7,7-dioxide monohydrochloride	22.26 g	22.26 g	1.113 g
10	(S)-(-)-1-(<u>tert</u> -butylamino)- 3-[(4-morpholino-1,2,5- thiadiazol-3-yl)oxy]-2- propanol maleate	6.834 g	1.367 g	6.834 g
15	Sodium citrate.2H ₂ O	2.940 g	2.940 g	2.940 g
	Benzalkonium Chloride	0.075 g	0.075 g	0.075 g
	Hydroxyethylcellulose	5.00 g	5.00 g	5.00 g
20	Sodium hydroxide q.s.	pH = 6.0	pH = 6.0	pH = 6.0
	Mannitol	16.00 g	21.00 g	35.90 g
25	Water for injection q.s. ad.	1000 g	1000 g	1000 g

The active compounds, sodium citrate,
 benzalkonium chloride (in a 50% W/W solution), and
 mannitol are dissolved in approximately 400 mL water
 for injection in a tared and sterile vessel. The pH
 30 of the composition is adjusted to 6.0 by addition of
 0.2 N sodium hydroxide solution, and water for
 injection is added until the weight of composition

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equals 750 g. The composition is sterilized by
 filtration, pushing the solution with a 2 bar
 pressure of 0.45 micron filtrated nitrogen. Then
 250 g of a 2% hydroxyethylcellulose autoclaved
 solution is added and the obtained solution is
 homogenized by stirring with a magnetic stirring
 bar. The solution is aseptically subdivided into
 3.5 mL aliquots and sealed.

10

EXAMPLE 32

<u>SOLUTION COMPOSITION</u>	<u>I</u>	<u>II</u>
(S,S)-(-)-5,6-dihydro-4-ethyl- amino-6-propyl-4H-thieno- [2,3b]thiopyran-2-sulfonamide- 7,7-dioxide monohydrochloride	2.0 mg	0.2 mg
(S)-(-)-1-(tert -butylamino)- 3-[(4-morpholino-1,2,5- thiadiazol-3-yl)oxy]-2- propanol maleate	0.5 mg	0.5 mg
GELRITE™ gellan gum	6.0 mg	6.0 mg
Monobasic sodium phosphate .2H ₂ O Dibasic sodium phosphate .12H ₂ O	Quantity sufficient to give final pH 5.5 - 6.0	
Benzyl dodecinium bromide	0.10 mg	0.10 mg
Polysorbate 80	0.2 mg	0.2 mg

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Water for injection q.s. ad. 1.0 mL 1.0 mL

5 The active compounds, GELRITE™ gellan gum,
phosphate buffer salts, benzyldodecinium bromide and
Polysorbate 80 are added to and suspended or dissolved in
water. The pH of the composition is adjusted to 5.5-6.0
and diluted to volume. The composition is rendered
sterile by ionizing radiation.

10

EXAMPLE 33

Study of (S,S)-(-)-5,6-dihydro-4-ethylamino-6-methyl-
4H-thieno[2,3b]thiopyran-2-sulfonamide-7,7-dioxide
15 (I) in combination with Timolol

Patients aged 40 or over, with either ocular
hypertension or primary open angle glaucoma with an
intraocular pressure (IOP) in one or both eyes of 22
20 mmHg or more at one time point each day while
receiving timolol 0.5% twice a day (bid) alone were
admitted to the study. Patients had been on timolol
0.5% bid, either alone or in combination for at least
three weeks prior to study entry and had been on
25 timolol 0.5% bid as their sole glaucoma therapy for
at least two weeks prior to study admission.

Secondary glaucoma was an exclusion as was a
history of glaucoma surgery or laser
trabeculoplasty/gonioplasty. Patients for whom
30 timolol was contraindicated by the datasheet were
excluded and also excluded were those on a concurrent

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B-blocker, carbonic anhydrase inhibitor, or clonidine. Thirty-one patients entered the study.

Procedure

- 5 1. All patients had their visual fields plotted by Goldmann Perimetry prior to study entry.
2. Patients were admitted for a 12 hour diurnal curve (i.e., IOP recorded at 08.00, 09.00, 10.00, 12.00, 14.00, 16.00, 18.00, 20.00 hours
10 approximately, the 08.00 recording was immediately prior to instillation of the drops). All pressures were measured by the same observer using the same Goldmann applanation tonometer.
- 15 3. Following recording of the baseline Diurnal Curve on timolol 0.5% bid, all of the patients were instructed to add 1 drop of a solution to each eye at 8:10 pm and 8:10 am, ten minutes after
20 adding timolol, for seven days. The solution given to 16 of the patients contained 2% Compound I; the solution given to the other 15 patients was a placebo solution.
- 25 4. On Day 2, the IOP of each patient was measured at 8 am and 9 am, and a 12 hour diurnal curve was recorded on Day 8.

preliminary IOP data follow:

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MEAN IOP PRESTUDY AND
PERCENT CHANGE IN IOP ON DAY 8 FROM PRESTUDY

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COMPOUND I PLUS TIMOLOL GROUP

	<u>TIMOLOL</u>	<u>TIMOLOL PLUS</u>
<u>TIME</u>	<u>BASELINE</u>	<u>COMPOUND I</u>
8am	27.4	-16.8 %
9am	27.1	-21.0 %
10	10am	-18.9 %
	noon	-17.3 %
	2pm	-18.6 %
	4pm	-17.0 %
	6pm	-18.2 %
15	8pm	-13.2 %

PLACEBO PLUS TIMOLOL GROUP

	<u>TIMOLOL</u>	<u>TIMOLOL PLUS</u>
<u>TIME</u>	<u>BASELINE</u>	<u>PLACEBO</u>
20	8am	- 3.4 %
	9am	- 4.5 %
	10am	- 1.7 %
	noon	+ 0.2 %
	2pm	+ 0.1 %
25	4pm	- 0.1 %
	6pm	- 3.7 %
	8pm	+ 6.6 %

30 These data are represented graphically in Figure 1.

Overall, Compound I given every 12 hours demonstrated a clinically and statistically

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significant effect over the effect of timolol alone,
ranging from 13%-21% based on worse eye analysis.

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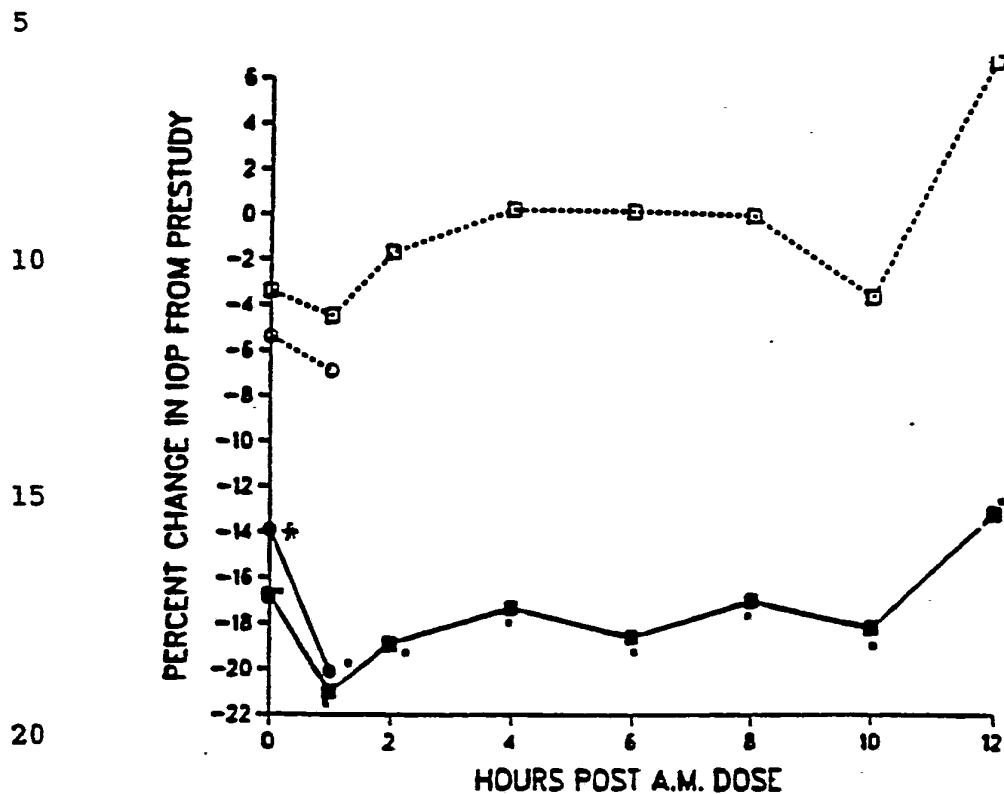
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2% Compound I in Combination with Timolol Bid

Mean Percent Change in IOP from Prestudy



• Significantly different from placebo ($p < 0.01$)
+ Significantly different from placebo ($p = 0.05$)

FIGURE 1

● + 2% COMPOUND I BID DAY 2
■ + 2% COMPOUND I BID DAY 8
○ + PLACEBO BID DAY 2
□ + PLACEBO BID DAY 8

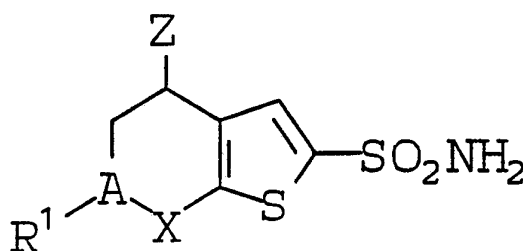
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WHAT IS CLAIMED IS:

1. An ophthalmic formulation for the treatment of ocular hypertension in a subject in need thereof, comprising an ophthalmologically acceptable carrier, 0.5 to 5% (w/w) of a carbonic anhydrase inhibitor or an ophthalmologically acceptable salt thereof and 0.01 to 1.0% of a β -adrenergic antagonist or an ophthalmologically acceptable salt thereof.

2. The formulation of Claim 1 wherein the concentration of carbonic anhydrase inhibitor is 0.5 to 3% and the concentration of the β -adrenergic antagonist is 0.1 to 0.5%.

3. The ophthalmic formulation of Claim 1 or 2 for the treatment of ocular hypertension comprising an ophthalmologically acceptable carrier, 0.05 to 5% of a carbonic anhydrase inhibitor of the structure:



the individual diastereomers, the individual enantiomers or mixtures thereof, or an ophthalmologically acceptable salt thereof, wherein:

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A is carbon or nitrogen;

Z is -NHR or -OR;

R is C₁₋₆ alkyl, either straight or branched chain;

R¹ is

- 5 (a) hydrogen,
 (b) C₁₋₃ alkyl, or
 (c) C₁₋₄ alkoxy-C₁₋₄ alkyl; and

10 X is -SO₂- or -C(=O)-;

 and 0.01 to 1.0% of a β -adrenergic antagonist
 selected from betaxolol, bufenolol, carteolol,
 levobunolol, metipranolol, and timolol, or an
15 ophthalmologically acceptable salt thereof.

 4. The formulation of Claim 3 wherein A is
 carbon, Z is -NHR, and X is -SO₂-.

20 5. The formulation of Claim 3 or 4 wherein:
 R is

- a) -CH₂CH₃,
 b) -CH₂CH₂CH₃, or
 c) -CH₂CH(CH₃)₂;

25 R¹ is

- a) hydrogen,
 b) -CH₃,
 c) -CH₂CH₂CH₃,
 d) -CH₂CH₂CH₂OCH₃, or
30 e) -CH₂OCH₂CH₃.

 6. The formulation of Claim 1, 2, 3, 4 or 5
 wherein β -adrenergic antagonist is timolol or an
 ophthalmologically acceptable salt thereof.

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7. The formulation of Claim 3, 4, 5, or 6 wherein A is carbon; and wherein: R is $-\text{CH}_2\text{CH}_3$ and R^1 is $-\text{CH}_3$; or R is $-\text{CH}_2\text{CH}_2\text{CH}_3$ and R^1 is $-\text{CH}_2\text{CH}_2\text{CH}_2\text{OCH}_3$; or R is $-\text{CH}_2\text{CH}_3$ and R^1 is $-\text{CH}_2\text{CH}_2\text{CH}_3$; or R is $-\text{CH}_2\text{CH}_2(\text{CH}_3)_2$ and R^1 is hydrogen; or R is $-\text{CH}_2\text{CH}_3$ and R^1 is $-\text{CH}_2\text{OCH}_2\text{CH}_3$; and carbons 4 and 6 of the carbonic anhydrase inhibitor both have S absolute stereochemical configuration.

8. The formulation of Claim 7 wherein the concentration of carbonic anhydrase inhibitor is 0.7 or 2.0%, and the concentration of timolol is 0.5%.

9. The formulation of Claim 1, 2, 3, 4, 5, 6, 7 or 8 further comprising 0.1% to 2% gellan gum.

10. A method of treating ocular hypertension which comprises the topical ocular administration to a patient in need of such treatment of a unit dose of the formulation of Claim 1, 2, 3, 4, 5, 6, 7, 8 or 9.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US92/02903

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :A61K 31/38,31/40, 31/44,31/50,31/535

US CL :514/232.5,232.8,253,278,409,431,433,443

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. :

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A,4,863,922 (BALDWIN) 05 September 1989, See column 13, lines 65-68.	1-10

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:		
"A"	document defining the general state of the art which is not considered to be part of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"E"	earlier document published on or after the international filing date	"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"O"	document referring to an oral disclosure, use, exhibition or other means	
"P"	document published prior to the international filing date but later than the priority date claimed	"&" document member of the same patent family

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