Part 2
to
EXHIBIT G

5,725,887, the disclosure of which is incorporated in its entirety herein by reference.

Preservatives other than oxidative preservative components may be included in the compositions. The choice of preservatives may depend on the route of administration. Preservatives suitable for compositions to be administered by one route may possess detrimental properties which preclude their administration by another route. For nasal and ophthalmic compositions, preferred preservatives include quaternary ammonium compounds, in particular the mixture of alkyl benzyl dimethyl ammonium compounds and the like known generically as "benzalkonium chloride." For compositions to be administered by inhalation, however, the preferred preservative is chlorbutol and the like. Other preservatives which may be used, especially for compositions to be administered rectally, include alkyl esters of p-hydroxybenzoic acid and mixtures thereof, such as the mixture of methyl, ethyl, propyl, butyl esters and the like which is sold under the trade name "Nipastat."

In another broad aspect of the present invention, compositions are provided which comprise an alpha-2-adrenergic agonist component, a preservative component in an effective amount to at least aid in preserving , preferably in an amount effective to preserve, the compositions and a liquid carrier component. Preferably, the preservative components include oxy-chloro components, such as compounds, ions, complexes and the like which (1) do not substantially or significantly detrimentally affect the alpha-2-adrenergic agonist components in the compositions or the patients to whom the compositions are administered, and (2) are substantially biologically acceptable and chemically stable. Such compositions in accordance with the present invention comprise an alpha-2-

adrenergic agonist component, an oxy-chloro component, and a liquid carrier component, and preferably are substantially free of cyclodextrins.

The carrier components useful in the present invention are selected to be non-toxic and have no substantial detrimental effect on the present compositions, on the use of the compositions or on the human or animal to whom the compositions are administered. In one embodiment, the carrier component is a liquid carrier. In a preferred embodiment, the carrier component is a liquid aqueous carrier component. A particularly useful aqueous liquid carrier component is that derived from saline, for example, a conventional saline solution or a conventional buffered saline solution. The aqueous liquid carrier preferably has a pH in the range of about 6 to about 9 or about 10, more preferably about 6 to about 8, and still more preferably about 7.5. The liquid medium preferably has an ophthalmically acceptable tonicity level, for example, of at least about 200 mOsmol/kg, more preferably in the range of about 200 to about 400 mOsmol/kg. In an especially useful embodiment, the osmolality or tonicity of the carrier component substantially corresponds to the tonicity of the fluids of the eye, in particular the human eye.

In one embodiment, the carrier components containing the SECs and the alpha-2-adrenergic agonist components may have viscosities of more than about 0.01 centipoise (cps) at 25°C, preferably more than about 1 cps at 25°C, even more preferably more than about 10 cps at 25°C. In a preferred embodiment, the composition has a viscosity of about 50 cps at 25°C and comprises a conventional buffer saline solution, a carboxymethylcellulose, and a Brimonidine tartrate.

In order to insure that the pH of the aqueous liquid

carrier component, and thus the pH of the composition, is maintained within the desired range, the aqueous liquid carrier component may include at least one buffer component. Although any suitable buffer component may be employed, it is preferred to select such component so as not to produce a significant amount of chlorine dioxide or evolve significant amounts of gas, such as CO_2. It is preferred that the buffer component be inorganic. Alkali metal and alkaline earth metal buffer components are advantageously used in the present invention.

Any suitable ophthalmically acceptable tonicity component or components may be employed, provided that such component or components are compatible with the other ingredients of the liquid aqueous carrier component and do not have deleterious or toxic properties which could harm the human or animal to whom the present compositions are administered. Examples of useful tonicity components include sodium chloride, potassium chloride, mannitol, dextrose, glycerin, propylene glycol and mixtures thereof. In one embodiment, the tonicity component is selected from inorganic salts and mixtures thereof.

The present compositions may conveniently be presented as solutions or suspensions in aqueous liquids or non-aqueous liquids, or as oil-in-water or water-in-oil liquid emulsions. The present compositions may include one or more additional ingredients such as diluents, flavoring agents, surface active agents, thickeners, lubricants, and the like, for example, such additional ingredients which are conventionally employed in compositions of the same general type.

The present compositions in the form of aqueous suspensions may include excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium

carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gun tragacanth and gun acacia; dispersing or wetting agents may be a naturally occurring phosphatide, for example, lecithin, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol mono-oleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example, polyoxyethylene sorbitan mono-oleate, and the like and mixtures thereof. Such aqueous suspensions may also contain one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose, saccharin, and the like and mixtures thereof.

The present compositions in the form of oily suspensions may be formulated in a vegetable oil, for example, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. Such suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation.

The present compositions may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example, olive oil or arachis oil, or a mineral oil, for example, liquid paraffin, and the like and mixtures thereof. Suitable emulsifying agents may be naturally-occurring gums, for example, gum acacia or gun tragacanth, naturally-occurring phosphatides, for example, soya bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example,

sorbitan mono-oleate, and condensation products of the said partial esters with ethylene oxide, for example, polyoxyethylene sorbitan mono-oleate. The emulsions may also contain sweetening and flavoring agents.

The present compositions in the form of syrups and elixirs may be formulated with sweetening agents, for example, as described elsewhere herein. Such formulations may also contain a demulcent, and flavoring and coloring agents.

The specific dose level for any particular human or animal depends upon a variety of factors including the activity of the active component employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination and the severity of the particular condition undergoing therapy.

In one broad aspect of the invention, complexes are formed in the present compositions. In one embodiment, the complexes include at least one monomer unit of a quinoxaline component. Examples of quinoxaline components include quinoxaline, (2-imidozolin-2-ylamino) quinoxaline, 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, salts thereof, esters thereof, other derivatives thereof, and the like and mixtures thereof. For example, in one embodiment, a complex of the present invention may include a conjugation of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline monomer units. In another embodiment, the complex may include a conjugation of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline monomer units and Brimonidine tartrate monomer units.

In a preferred embodiment, the complexes of the present invention are dimers. For example, a dimer in accordance with the present invention may include a quinoxaline and a 5-bromo-6-(2-imidozolin-2-ylamino)

quinoxaline. Preferably, a dimer in accordance with the present invention includes two Brimonidine tartrate monomer units.

Without wishing to limit the invention to any theory or mechanism of operation, it is believed that any peroxide forming agent or strong oxidizing agent such as the oxidative preservative components, for example oxy-chloro components, peroxides, persalts, peracids, and the like, and mixtures thereof may facilitate the formation of the complexes, preferably complexes of alpha-2-adrenergic agonist components. For example, dimers of Brimonidine tartrate monomer units are believed to be formed in the presence of chlorites, preferably stabilized chlorine dioxide.

Furthermore, it is believed that the interactions between the monomers which serve to hold the monomers or monomer subunits together to form a complex, preferably an oligomer and more preferably a dimer, may include, but not limited to, covalent bonding, ionic bonding, hydrophobic bonding, electrostatic bonding, hydrogen bonding, other chemical and/or physical interactions, and the like and combinations thereof. Such complexes may disassociate in liquid, for example, aqueous liquid, media. In one embodiment, the monomers or monomer subunits are held together by other than covalent bonding. In one embodiment, the monomers or monomer subunits are held together by electrostatic bonding or forces.

The following non-limiting examples illustrate certain aspects of the present invention.

EXAMPLE 1

Brimonidine tartrate has a pKa of about 7.78. The pH-solubility profile of 0.5% (w/v) Brimonidine tartrate in a formulation, Ophthalmic Solution, was established in

the pH range of about 5 to about 8 at 23 °C. Table 1. It will be understood that concentrations of adrenergic agonists other than 0.5% may be used, so long as they have therapeutic activity. Likewise, the temperature may be varied, for example, solubility curves may be performed at 37 °C (98.6 °F). The formulation vehicle was prepared by first dissolving polyvinyl alcohol (PVA) in water. The PVA was added to approximately 1/3 of the required total amount of purified water with constant stirring. The slurry was stirred for 20-30 minutes and then heated to 80-95 °C with constant stirring. The mixture was removed from the heat source within 1 hour after having reached the temperature of 80-90 °C and stirred for an additional 10 minutes to ensure homogeneity (Part I). The other ingredients of the Ophthalmic Solution, except for Brimonidine tartrate, were dissolved in a separate container with an additional 1/3 of the required total amount of purified water (Part II). The PVA mixture (Part I) was then quantitatively transferred to Part II using several rinse volumes of purified water. The solution was adjusted to final volume with purified water without pH adjustment.

Brimonidine tartrate was weighed and transferred to a 10 mL test tube containing 5 mL of the formulation vehicle described above. The pH of each sample was then adjusted to a desired value using dilute sodium hydroxide and/or dilute hydrochloric acid. The samples were placed in a rack on a stir plate and stirred at high speed to achieve uniform mixing for 2 days; a partition was placed between the rack and the stir plate to prevent any heat diffusion from the stir plate to the samples. The temperature of the laboratory was monitored throughout the study and was found to be 23±1 °C.

At the end of two days of stirring, the pH value of

each sample was measured, and then approximately 1 mL of each sample was placed in a micro centrifuge tube (polypropylene) and centrifuged at 4,000 rpm for 10 minutes. The supernatant was filtered through a 1μm filter unit (Whatman, 13mm, PTFE). The first 3-4 drops of the filtrate were discarded; the rest of the filtrate was received and diluted quantitatively with HPLC mobile phase. The dilute sample was then injected directly on the HPLC column (Dupont Zorbax, 250mm x 4.6mm, 5μm) for Brimonidine tartrate assay in order to quantify the amount of Brimonidine tartrate. A control of 10.05% Brimonidine tartrate was prepared in the formulation vehicle at pH 6.3-6.5 and assayed before (untreated) and after (treated) centrifugation and filtration. This was done to evaluate the potential loss of Brimonidine tartrate in these two steps of the sample preparation. To ensure reproducibility, the study was repeated on consecutive days.

Table I. 0.5% Brimonidine tartrate in Ophthalmic Solution.

Ingredient	Percent (w/v)
Brimonidine tartrate	0.50
Benzalkonium Chloride, NF	0.0050
Polyvinyl Alcohol, USP	1.4
Sodium Chloride, USP	0.66
Sodium Citrate, Dihydrate, USP	0.45
Hydrochloric Acid, NF or Sodium Hydroxide, NF for pH adjustment	5-8
Purified Water, USP	QS

The solubility data for Brimonidine tartrate in the formulation vehicles are presented in Table II. The results show that the solubility of Brimonidine tartrate

is highly pH-dependent and spans more than two orders of magnitude over the pH range of 5-8. The solubility decreases sharply as the pH increases. The results for the treated and untreated controls are very close, suggesting that centrifugation and filtration does not cause any significant loss of Brimonidine tartrate. The two solubility profiles obtained on consecutive days agree with each other.

Table II. Solubility of Brimonidine tartrate in the Ophthalmic Solution Over pH Range of 5 to 8.

	STUDY 1		STUDY 2	
Sample	pH[a]	Solubility[a]	pH[a]	Solubility[a]
1	5.55	≥164.4[b]	5.50	≥200.6[b]
2	5.92	132.6	5.92	160.8
3	6.14	30.4	6.06	50.1
4	6.57	7.55	6.90	3.19
5	7.00	2.69	7.40	1.19
6	7.45	1.17	7.77	0.63
7	7.83	0.62	7.86	0.58
8	—	—	7.88	0.54
Control/ (untreated)	—	0.486[c]	—	—
Control/ (treated)	—	0.484[d]	—	—

[a] Measured after stirring for two-days before sample withdrawal for centrifugation and filtration.

[b] Represents theoretical concentration based on sample weight. The sample solution was clear indicating that all of the Brimonidine tartrate had dissolved.

[c] Concentration of Brimonidine tartrate in

control before centrifugation and filtration step.

[d] Concentration of Brimonidine tartrate in control after centrifugation and filtration step.

[e] %w/v.

EXAMPLE 2

The pH-solubility profiles of Brimonidine tartrate in compositions (solutions) containing SECs and oxy-chloro components were determined. Particularly, the effects of sodium carboxymethylcellulose (CMC), an SEC, on the solubility of Brimonidine tartrate at various pH conditions were determined. The various concentrations of CMC tested with Brimonidine tartrate were 0%, 0.056%, 0.17%, 0.5%, 1.5% (w/v), Table III.

The samples tested also contained isotonic components, buffer components, and stabilized chlorine dioxide (Purite™), Table III. Sodium carboxymethyl-cellulose, sodium chloride, potassium chloride, calcium chloride dihydrate, and magnesium chloride hexahydrate were USP grade. Boric acid and sodium borate decahydrate were NF grade.

Table III

	Sample 1	Sample 2	Sample 3	Sample 4	Sample 5	
Brimonidine tartrate	0.2%	0.2%	0.2%	0.2%	0.2%	(w/v)
CMC	0.0%	0.056%	0.17%	0.5%	1.5%	(w/v)
Stabilized chlorine dioxide[a]	0.005%	0.005%	0.005%	0.005%	0.005%	(w/v)
Sodium chloride	0.58%	0.58%	0.58%	0.58%	0.58%	(w/v)
Potassium chloride	0.14%	0.14%	0.14%	0.14%	0.14%	(w/v)
Calcium chloride, dihydrate	0.02%	0.02%	0.02%	0.02%	0.02%	(w/v)
magnesium chloride, hexahydrate	0.006%	0.006%	0.006%	0.006%	0.006%	(w/v)
boric acid	0.2%	0.2%	0.2%	0.2%	0.2%	(w/v)
sodium tetraborate, decahydrate	0.14%	0.14%	0.14%	0.14%	0.14%	(w/v)

[a] Sold under the trademark Purite™ by Allergan, Inc.

Each sample (1 through 5) was subjected to a range of pH's from about 7 to about 10. The vials containing the sample solutions were placed on a laboratory rotator and left for equilibration for fifteen days at room temperature (~21 °C). The sample solutions were filtered using a 25 mm diameter polysulfone cellulose acetate syringe type filter with 0.45μm pore size. The filtered solutions were assayed for Brimonidine.

Conventional HPLC and detection techniques were used to detect and determine the concentrations of soluble Brimonidine tartrate. Table IV. The solubility is plotted against pH for each CMC concentration. The experimental data points were fitted to a modified Henderson-Hasselbalch equation using a nonlinear least squares routine (Deltagraph version 4.0 DeltaPoint, Inc.), Fig. 1. The R^2 values show the goodness of fit between the experimental values and the theoretical equation to be better than 0.991.

Table IV

Solubility of Brimonidine tartrate (%)

pH	0%CMC	0.056%CMC	0.17%CMC	0.5%CMC	1.5%CMC
6.67		0.9302		1.4464	
6.68	1.4256		1.4200		
6.93			0.7302		
7.10				0.3693	
7.11	0.2064	0.2828			
7.35					0.1904
7.56				0.1451	
7.68	0.0786				
7.77		0.0721			
7.81			0.0735		
8.10					0.0498
8.46				0.0313	
8.50	0.0286				
8.55			0.0328		
8.67					0.0311
9.93		0.0234			
9.94				0.0250	
10.05			0.0241		
10.09	0.0218				
10.11					0.0222

Fig. 1 clearly shows that the solubility of Brimonidine tartrate tends to increase with increasing CMC concentrations. For example, at pH 7.5, the sample with 0% CMC resulted in 1000 ppm of Brimonidine tartrate; 0.056% CMC, 1300 ppm; 0.17% CMC, 1300 ppm; and 0.5%, 1600 ppm. At pH 7.5, the sample with 1.5% CMC resulted in about 1400 ppm, which is less than that of a similar solution with CMC at 0.5%. It is unclear at this point

what the cause of this observation may be. Nonetheless, Brimonidine tartrate is more soluble in solution with a 1.5% CMC than with no CMC.

CMC is also effective to solubilize Brimonidine tartrate in a biological environment, for example the biological environment of the cornea.

EXAMPLE 3

Brimonidine tartrate dimers.

Brimonidine tartrate is added to a test tube containing a composition including chlorite. The test tube was allowed to equilibrate for ten days. Samples obtained from the test tube is analyzed. It is observed that a portion of the Brimonidine tartrate monomer units conjugated to form dimers.

While this invention has been described with respect to various specific examples and embodiments, it is to be understood that the invention is not limited thereto and that it can be variously practiced with the scope of the following claims.

WHAT IS CLAIMED IS:

1. A composition comprising:

an alpha-2-adrenergic agonist component in an amount effective to provide a therapeutic benefit to a patient to whom the composition is administered;

a solubility enhancing component in an amount effective to increase the solubility of the alpha-2-adrenergic agonist component in the composition relative to the solubility of an identical alpha-2-adrenergic agonist component in a similar composition without the solubility enhancing component; and

a liquid carrier component.

2. The composition of claim 1 wherein the alpha-2-adrenergic agonist component is selected from the group consisting of imino-imidazolines, imidazolines, imidazoles, azepines, thiazines, oxazolines, guanidines, catecholamines, derivatives thereof and mixtures thereof.

3. The composition of claim 1 wherein the therapeutically active component includes a quinoxaline component.

4. The composition of claim 3 wherein the quinoxaline component is selected from the group consisting of quinoxaline, derivatives thereof, and mixtures thereof.

5. The composition of claim 3 wherein the quinoxaline component is selected from the group consisting of quinoxaline, (2-imidozolin-2-ylamino) quinoxaline, 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, and tartrate of 5-bromo-6-(2-imidozolin-2-

ylamino) quinoxaline, derivatives thereof and mixtures thereof.

6. The composition of claim 1 wherein the therapeutically active component comprises a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline.

7. The composition of claim 1 wherein the alpha-2-adrenergic agonist component is substantially unionized.

8. The composition of claim 1 wherein the alpha-2-adrenergic agonist component is substantially unionized in a biological environment to which the composition is administered.

9. The composition of claim 1 wherein the alpha-2-adrenergic agonist component has increased diffusion through a lipid membrane relative to an identical alpha-2-adrenergic agonist component in a similar composition without the solubility enhancing component.

10. The composition of claim 1 wherein the alpha-2-adrenergic agonist component is selected from the group consisting of agonists of alpha-2A-adrenergic receptors, agonists of alpha-2B-adrenergic receptors, agonists of alpha-2D-adrenergic receptors and mixtures thereof.

11. The composition of claim 1 wherein the solubility enhancing component is effective to increase the solubility in a biological environment of the alpha-2-adrenergic agonist component relative to the solubility in a biological environment of an identical alpha-2-adrenergic agonist component in a similar composition without the solubility enhancing component.

12. The composition of claim 1 wherein the solubility enhancing component comprises a polyanionic component.

13. The composition of claim 12 wherein said polyanionic component is selected from the group consisting of anionic cellulose derivatives, anionic polymers derived from acrylic acid, anionic polymers derived from methacrylic acid, anionic polymers derived from alginic acid, anionic polymers derived from amino acids and mixtures thereof.

14. The composition of claim 1 wherein the solubility enhancing component is selected from the group consisting of anionic cellulose derivatives and mixtures thereof.

15. The composition of claim 1 wherein the solubility enhancing component is selected from the group consisting of carboxymethylcelluloses and derivatives thereof.

16. The composition of claim 1 wherein the solubility enhancing component is present in an amount in a range of about 0.1% (w/v) to about 30% (w/v).

17. The composition of claim 1 wherein the solubility enhancing component is present in an amount in a range of about 0.2% (w/v) to about 10% (w/v).

18. The composition of claim 1 wherein the solubility enhancing component is present in an amount in a range of about 0.2% (w/v) to about 0.6% (w/v).

19. The composition of claim 1 wherein the liquid carrier component is an aqueous liquid carrier component.

20. The composition of claim 1 which is a solution.

21. The composition of claim 1 which has a pH of about 7 or greater.

22. The composition of claim 1 which has a pH in a range of about 7 to about 9.

23. The composition of claim 1 which is ophthalmically acceptable.

24. A composition comprising:

an alpha-2-adrenergic agonist component in an amount effective to provide a therapeutic benefit to a patient to whom the composition is administered;

an anionic cellulose derivative in an amount effective to increase the solubility of the alpha-2-adrenergic agonist component; and

an aqueous liquid carrier component.

25. The composition of claim 24 wherein the alpha-2-adrenergic agonist component comprises a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline.

26. The composition of claim 24 wherein the anionic cellulose derivative comprises carboxymethylcellulose.

27. The composition of claim 24 wherein the anionic cellulose derivative is present in an amount in a range of about 0.2% (w/v) to about 0.6% (w/v).

28. A composition comprising:

a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline in an amount effective to provide a therapeutic benefit to a patient to whom the composition is administered;

a solubility enhancing component in an amount effective to increase the solubility of the tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline; and

an aqueous liquid carrier component.

29. The composition of claim 28 wherein the solubility enhancing component comprises a carboxymethylcellulose.

30. The composition of claim 28 which is ophthalmically acceptable.

31. A complex comprising monomer units derived from one or more quinoxaline components.

32. The complex of claim 31 wherein the quinoxaline component is selected from the group consisting of a quinoxaline, a (2-imidozolin-2-ylamino) quinoxaline, a 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, derivatives thereof and mixtures thereof.

33. The complex of claim 31 wherein the quinoxaline component is a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline.

34. An oligomer comprising monomer units derived from a quinoxaline component.

35. The oligomer of claim 34 wherein the quinoxaline component is selected from the group consisting of a quinoxaline, a (2-imidozolin-2-ylamino) quinoxaline, a 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline, derivatives thereof and mixtures thereof.

36. The oligomer of claim 34 wherein the quinoxaline component is a tartrate of 5-bromo-6-(2-imidozolin-2-ylamino) quinoxaline.

37. The oligomer of claim 34 which is a dimer.

38. The oligomer of claim 35 which is a dimer.

39. The oligomer of claim 36 which is a dimer.

40. A composition comprising:

an alpha-2-adrenergic agonist component in an amount effective to provide a therapeutic benefit to a patient to whom the composition is administered;

an oxy-chloro component in an effective amount to at least aid in preserving the composition; and

a liquid carrier component,

wherein the composition is substantially free of cyclodextrins.

41. The composition of claim 40 wherein the alpha-2-adrenergic agonist component is selected from the group consisting of imino-imidazolines, imidazolines, imidazoles, azepines, thiazines, oxazolines, guanidines, catecholamines, derivatives thereof and mixtures thereof.

42. The composition of claim 40 wherein the

therapeutically active component includes a quinoxaline component.

43. The composition of claim 42 wherein the quinoxaline component is selected from the group consisting of quinoxaline, derivatives thereof, and mixtures thereof.

44. The composition of claim 40 which further includes a solubility enhancing component in an amount effective to increase the solubility of the alpha-2-adrenergic agonist component in the composition relative to the solubility of an identical alpha-2-adrenergic agonist component in a similar composition without the solubility enhancing component.

45. The composition of claim 44 wherein the solubility enhancing component is effective to increase the solubility in a biological environment of the alpha-2-adrenergic agonist component relative to the solubility in a biological environment of an identical alpha-2-adrenergic agonist component in a similar composition without the solubility enhancing component.

46. The composition of claim 44 wherein the solubility enhancing component comprises a polyanionic component.

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DECLARATION FOR PATENT APPLICATION

D-2892

As a below named inventor, I hereby declare that:

My residence post office address and citizenship are as stated below next to my name.
I believe I am the original first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled **COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS** the specification of which

(check one) [X] is attached hereto
[ ] was filed on
as US Application Serial Number or PCT International Application Number
and was amended on ___ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.
I acknowledge the duty to disclose information which is material to the patentability as defined in 37 CFR § 1.56.
I hereby claim foreign priority benefits under 35 U.S.C. §119(a)-(d) or §365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed. NONE

Prior Foreign Application(s)			Priority Not Claimed [ ]
(Number)	(Country)	(Day/Month/Year Filed)	

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

60/218,200	July 14, 2000
(Application Number)	(Filing Date)

I hereby claim the benefit under 35 U.S.C. §120 of any United States application(s), or §365(c) of any PCT International application designation the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. §112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application. NONE

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I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: Martin A. Voet, Reg. No. 25,208, Robert Baran, Reg. No. 25,806, Carlos A. Fisher, Reg. No. 36,510, Stephen Donovan, Reg. No. 33,433 and Frank J. Uxa, Reg. No. 25,612

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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Internal Address: PO BOX 19534

Street Address: 2525 DUPONT DRIVE
IRVINE, CA 92612

Additional name(s) & address(es) attached? ☐ Yes ☒ No

3. Nature of conveyance:
☒ Assignment ☐ Merger
☐ Security Agreement ☐ Change of Name
☐ Other: _____
Execution Date: JULY 3RD AND 9TH, 2001

4. Application number(s) or patent number(s):
If this document is being filed together with a new application, the execution date of the application is: JULY 3 & 9, 2001
A. Patent Application No.(s)
B. Patent No. (s)
Additional numbers attached? ☐ Yes ☒ No

5. Name and address of party to whom correspondence concerning document should be mailed:
Name: ALLERGAN, INC.
Internal Address: PO BOX 19534
Street Address: 2525 DUPONT DRIVE
IRVINE, CA 92612

6. Total number of applications and patents involved: 1

7. Total fee (37 CFR 3.41).....$ 40
☐ Enclosed
X Authorized to be charged to deposit account

8. Deposit account number: 01-0885
(Attach duplicate copy of this page if paying by deposit account)

DO NOT USE THIS SPACE

9. Statement and signature.
To the best of my knowledge and belief, the foregoing information is true and correct and any attached copy is a true copy of the original document.

FRANK J. UXA
Name of Person Signing

Signature

July 10, 2001
Date

3
Total number of pages including cover sheet, attachments and document:

Mail documents to be recorded with required cover sheet information to:
Commissioner of Patents & Trademarks, Box assignments
Washington, D.C. 20231

10236566 .090602

OLEJNIK ET AL 1 Docket No. 17361(AP)

ASSIGNMENT

WHEREAS we, Orest Olejnik of ORANGE COUNTY, CALIFORNIA and Edward D.S. Kerslake of SUFFOLK COUNTY, MASSACHUSETTS (hereinafter referred to as ASSIGNOR), have invented and own a certain invention entitled: COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS for which I have executed a provisional application, and non-provisional application claiming priority thereto, for Letters Patent of the United States, said provisional patent application having been filed July 14, 2000 and bearing Serial No. 60/218,200 and said non-provisional application for which application for Letters Patent of the United States has been executed on even date herewith.

WHEREAS: Allergan Sales, Inc., having its principal place of business at 2525 Dupont Drive, Irvine, CA 92612 (hereinafter referred to as ASSIGNEE), is desirous of acquiring the entire interest in, to and under said invention and in, to and under Letters Patent or similar legal protection to be obtained therefor in the United States and in any and all foreign countries.

NOW, THEREFORE, TO ALL WHOM IT MAY CONCERN: Be it known that in consideration of the payment by ASSIGNEE TO ASSIGNOR of the sum of One Dollar ($1.00), the receipt of which is hereby acknowledged, and for other good and valuable consideration, ASSIGNOR hereby sells, assigns and transfers to ASSIGNEE the full and exclusive right, title and interest to said invention in the United States and its territorial possessions and in all foreign countries to all Letters Patent or similar legal protection in the United States and its territorial possessions and in any and all foreign countries to be obtained for said invention by said application or any continuation, divisional, renewal, substitute or reissue thereof or any legal equivalent thereof in a foreign country for the full term or terms for which the same may be granted.

ASSIGNOR hereby covenants that no assignment, sale, agreement or encumbrance has been or will be made or entered into which would conflict with this assignment and sale;

ASSIGNOR further covenants that ASSIGNEE will, upon its request, be provided promptly with all pertinent facts and documents relating to said application, said invention and said Letters Patent and legal equivalents in foreign countries as may be known and accessible to ASSIGNOR and will testify as to the same in any interference or litigation related thereto and will promptly execute and deliver to ASSIGNEE or its legal representative any and all papers, instruments or affidavits required to apply for, obtain, maintain, issue and enforce said application, said invention and said Letters Patent and said equivalent thereof in any foreign country which may be necessary or desirable to carry out the purposes thereof.

10236566.090602

OLEJNIK ET AL 2 Docket No. 17361(AP)

IN WITNESS WHEREOF, I/We have hereunto set hand and seal this

7/9, 2001.

OREST OLEJNIK

State of CALIFORNIA)
) ss:
County of ORANGE)

On JULY 9, 2001 before me, MARY LOU McNOWN
personally appeared OREST OLEJNIK
~~personally known to me~~ (or proved to me on the basis of satisfactory evidence) to be the person(~~s~~) whose name(~~s~~) is/~~are~~ subscribed to the within instrument and acknowledged to me that ~~he/she/they~~ executed the same in ~~his/her/their~~ authorized capacity(~~ies~~), and that by ~~his/her/their~~ signature(~~s~~) on the instrument the person, or the entity upon behalf of which the person(~~s~~) acted, executed the instrument.

WITNESS my hand and official seal.

MARY LOU MCNOWN
Commission # 1229524
Notary Public - California
Orange County
My Comm. Expires Aug 16, 2003

Mary Lou McNown
Notary Public

IN WITNESS WHEREOF, I/We have hereunto set hand and seal this

7/3, 2001.

EDWARD D.S. KERSLAKE

State of MASSACHUSETTS)
) ss:
County of Suffolk)

On July 3, 2001 before me, Maureen Vibert, Notary Public
personally appeared Edward D.S. Kerslake
personally known to me (or proved to me on the basis of satisfactory evidence) to be the person(s) whose name(s) is/are subscribed to the within instrument and acknowledged to me that he/she/they executed the same in his/her/their authorized capacity(ies), and that by his/her/their signature(s) on the instrument the person, or the entity upon behalf of which the person(s) acted, executed the instrument.

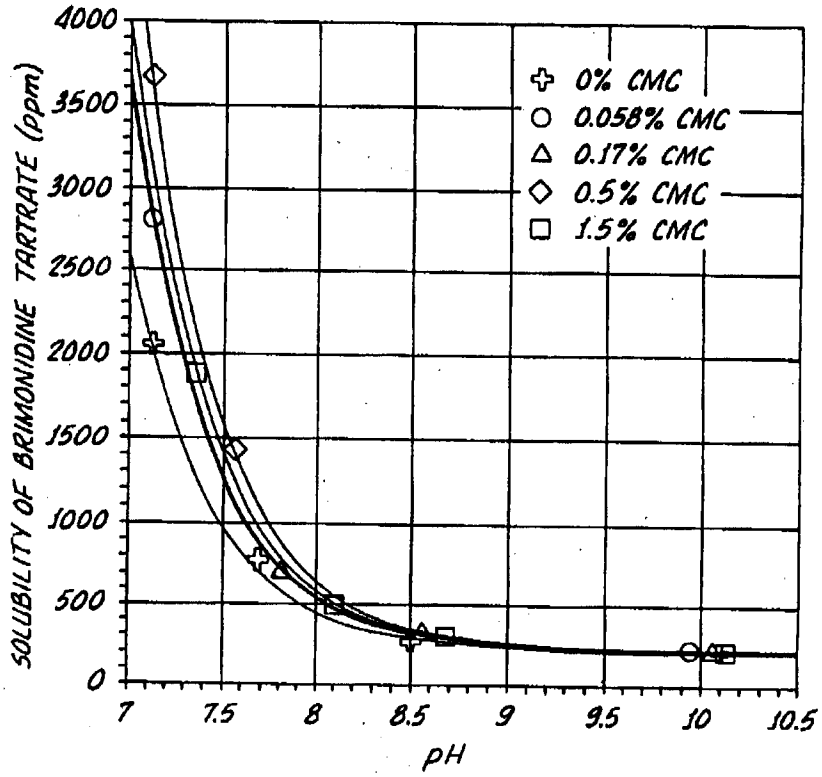
WITNESS my hand and official seal.

Maureen R Vibert
Notary Public
My Commission expires: 11/6/2006

10836566.090602

PRINT OF DRAWINGS
AS ORIGINALLY FILED

1/1



10236566.090602

APPLICATION DATA SHEET

Inventor Information

Inventor One Given Name::	Orest
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State or Province::	CA
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Citizenship Country::	USA

Inventor Two Given Name::	Edward D.S.
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Citizenship Country::	UK

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10236566 .090602

Application Information

Title Line One::	Compositions Containing Alpha-2-Adrenergic
Title Line Two::	Agonist Components
Total Drawing Sheets::	1
Formal Drawings?::	Yes
Application Type::	Utility

Representative Information

Registration Number One::	Frank J. Uxa, Jr..... 25,612
Registration Number Two::	Donald E. Stout..... 34,493
Registration Number Three::	Robert D. Buyan..... 32,460
Registration Number Four::	Kenton R. Mullins..... 36,331
Registration Number Five::	Jo Anne M. Ybaben..... 42,243
Registration Number Six::	Linda Allyson Fox..... 38,883
Registration Number Seven::	Kyle D. Yesland..... 45,520
Registration Number Eight::	Ketan Vakil..... 43,215
Registration Number Nine::	Greg S. Hollrigel, Ph. D..... 45,374
Registration Number Ten::	Martin A. Voet..... 25,208
Registration Number Eleven::	Robert J. Baran..... 25,806
Registration Number Twelve::	Carlos A. Fisher..... 36,510
Registration Number Thirteen::	Stephen Donovan..... 33,433

Continuity Information

This application is a::	Regular
>Application One::	60/218,200
Filing Date::	July 14, 2000
This application is a::	Continuation
>Application One::	09/904,018
Filing Date::	July 10, 2001

Assignment Information

10236566.090602

Assignee Name::	Allergan Sales, Inc.
Postal Address Line One::	2525 Dupont Drive
Postal Address Line Two::	
City::	Irvine
State or Province::	CA
Postal or Zip Code::	92612

9-9-02 10236566.090602 A $$

8(S 10/97)

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Docket No **D-2892CON**

Total Pages in this Submission

TO THE COMMISSIONER FOR PATENTS
Box Patent Application
Washington, D.C. 20231

Transmitted herewith for filing under 35 U.S.C. 111(a) and 37 CFR 1.53(b) is a new utility patent application for an invention entitled:

COMPOSITIONS CONTAINING ALPHA-2-ADRENERGIC AGONIST COMPONENTS

and invented by:

OLEJNIK ET AL

If a CONTINUATION APPLICATION, *check appropriate box an supply the requisite information:*
[xContinuation [ ]Divisional [ ]Continuation-in-part (CIP) of prior application No.: **09/904,018 filed July 10, 2001, which, in turn , claims the benefit of U.S. Provisional Application Serial No. 60/218,200, filed July 14, 2000.**

Enclosed are **Application Elements:**

[x] Filing Fee

[x] Specification having 40 page(s) and including the following:

- [x] Title of the Invention
- [X] Cross References to Related Applications *(if applicable)*
- [x] Background of the Invention
- [x] Brief Summary of the Invention
- [x] Description of the Drawings
- [x] Detailed Description
- [x] Claim(s) as Classified Below
- [x] Abstract of the Disclosure

[x] 1 Sheets of Drawings(s) (37 CFR 113) [X] Formal [ ] Informal

[x] Oath or Declaration [x] Executed [ ] Unexecuted
[x] Copy from prior application (37 CFR 1.63(d)) *(for continuation/divisional application only)*

[x] Power of Attorney [x] Executed [ ] Unexecuted
[x] Copy from prior application (37 CFR 1.63(d)) *(for continuation/divisional application only)*

[ ] Incorporation By Reference – The entire disclosure of the prior application from which a copy of the oath or declaration is supplied under the above entry, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

[ ] Computer Program in Microfiche *(Appendix)*

Accompanying Application Parts

[x] Assignment Papers (cover sheets & documents(s))
[x] The prior application is assigned of record to **Allergan Sales, Inc.**
[x] Copy from prior application (37 CFR 1.63(d)) *(for continuation/divisional application only)*

[ ] 37 CFR 3.73(B) Statement *(when there is an assignee)*