PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A01N 47/44, A61L 2/16, 2/18

A1

(11) International Publication Number: **WO 98/20738**

(43) International Publication Date: 22 May 1998 (22.05.98)

(21) International Application Number: PCT/US97/20087

(22) International Filing Date: 4 November 1997 (04.11.97)

(30) Priority Data:
60/031,646 13 November 1996 (13.11.96) US

(71) Applicant: BAUSCH & LOMB INCORPORATED [US/US]; One Bausch & Lomb Place, Rochester, NY 14604–2701 (US).

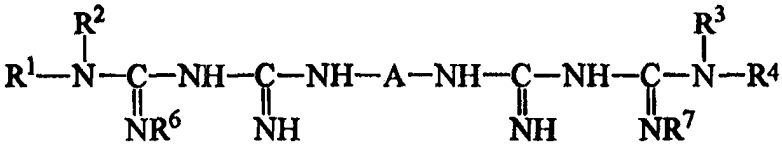
(72) Inventors: SPOONER, Susan, P.; 22 Saybrooke Drive, Penfield, NY 14526 (US). HEILER, David, J.; 173 Wadsworth Avenue, Avon, NY 14414 (US). SIMPSON, Lisa, C.; 73 Raton Avenue, Rochester, NY 14626 (US). MARSCH, David, A.; Apartment 2065, 5505 Cross Creek Lane, Fort Worth, TX 76109 (US).

(74) Agents: KONKOL, Chris, P. et al.; Bausch & Lomb Incorporated, One Bausch & Lomb Place, Rochester, NY 14604–2701 (US).

(81) Designated States: AL, AU, BB, BR, BY, CA, CU, EE, ES, FI, GB, HU, IL, JP, KE, KG, KP, KR, MD, MK, MN, MW, NO, NZ, PL, PT, RU, SE, SI, SK, TJ, TR, TT, UA, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: COMPOSITIONS AND METHODS IN WHICH BIS(BIGUANIDES) PROVIDE ENHANCED ANTIMICROBIAL EFFICACY FOR DISINFECTING CONTACT LENSES



(I)

(57) Abstract

The present invention is directed to an ophthalmically safe disinfecting solution for contact lenses comprising a bis(biguanide) having formula (I) wherein R^1 and R^4 are independently selected from the group consisting of branched or unbranched alkyl having 4–12 carbon atoms, ether or thioether radical having 4–12 carbon atoms, or cycloalkyl or cycloalkyl–alkyl radical having 5–12 carbon atoms; R^2 and R^3 are independently selected from the group consisting of hydrogen, alkyl having 1–12 carbon atoms, alkoxyalkyl having 1–12 carbon atoms, or cycloalkyl or cycloalkyl–alkyl having 5–12 carbon atoms; R^6 and R^7 are independently selected from the group consisting of hydrogen and alkyl radical having 1–6 carbon atoms, and A in the above formula is selected from the divalent radical having 4–16 carbon atoms consisting of a divalent alkyl, alkyloxyalkyl, alkylsulfide, or a polymethylene interrupted with a cyclic divalent radical. In one embodiment of the present invention, such biguanides may be combined with a polymeric biguanide for complementary or synergistic biocidal efficacy. The invention is also directed to an improved method of disinfecting a contact lens.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

COMPOSITIONS AND METHODS IN WHICH BIS(BIGUANIDES) PROVIDE ENHANCED ANTIMICROBIAL EFFICACY FOR DISINFECTING CONTACT LENSES

Field of the Invention

This invention relates to new and improved solutions for the treatment of contact lenses and to methods for treating contact lenses with such solutions. In particular, the present invention is directed to disinfecting solutions comprising certain bis(biguanides) and to their use in improved regimens for treating contact lenses.

Background of the Invention

Generally, contact lenses in wide use fall into three categories: (1) hard lenses formed from materials prepared by polymerization of acrylic esters, such as polymethyl methacrylate (PMMA), (2) rigid gas permeable (RGP) lenses formed from silicone acrylates and fluorosilicone methacrylates, and (3) gel, hydrogel or soft type lenses made of polymerized hydrophilic or hydrophobic monomers, such as 2-hydroxyethyl methacrylate (HEMA). The hard acrylic type contact lenses are characterized by low water vapor diffusion constants, resistance to the effects of light, oxygen and hydrolysis and absorb only minor amounts of aqueous fluids. Because of the durability of hard contact lenses, coupled with their tendency not to absorb appreciable amounts of water, the selection of suitable disinfecting agents, cleaning agents or other lens care compounds is relatively non-critical.

However, unlike hard lenses, soft type contact lenses and certain of the newer rigid gas permeable contact lenses have a tendency to bind and concentrate significantly more fluids, environmental pollutants, water impurities, as well as antimicrobial agents and other active ingredients commonly found in lens care solutions. In most instances, the low levels of the ingredients in lens care solutions do not lead to eye tissue irritation when used properly. Nevertheless, because of the inherent binding action of protein deposits to soft lens materials, some disinfecting agents and preservatives tend to build up on lens

surfaces and may become concentrated to potentially hazardous levels, such that when released could cause corneal inflammation and other eye tissue irritation.

Previous efforts to alleviate the problem of binding and concentrating disinfectants and preservatives onto contact lens surfaces, and reducing the potential for eye tissue irritation have not been totally satisfactory. For example, in spite of low toxicity levels, not all disinfectants are compatible for use with all types of contact lenses. Although they are effective antibacterial agents, their use can result in a loss of lens hydrophilic properties, cause solution instability or may even lack compatibility with certain types of hard lenses, e.g., high silicon content.

Certain antibacterial agents were found to be more compatible with contact lenses and exhibit less binding on lens surfaces. In one case, it was found that chlorhexidine, a biguanide, binds to soft lens material seven times less than benzalkonium chloride, but the presence of proteinaceous oily tear-film deposits on a lens can double the amount of chlorhexidine absorbed on the lens compared to a clean lens. U.S. patent 4,354,952 discloses very dilute disinfecting and cleaning solutions containing chlorhexidine or its salts in combination with certain amphoteric and non-ionic surfactants. These solutions were found to reduce the amount of binding of chlorhexidine on hydrophilic soft contact lenses. Notwithstanding the reduction in binding achieved by this invention, the use of chlorhexidine did result in certain tradeoffs. The antimicrobial activity of the chlorhexidine may be diminished when used with certain amphoteric surfactants. Furthermore, it was reported that if not used in proper ratio, the surfactant and disinfectant will precipitate unless a non-ionic type surfactant is also employed.

U.S. patent 4,361,548 discloses a contact lens disinfectant and preservative containing dilute aqueous solutions of a polymer; namely, polydimethyldiallylammonium chloride (DMDAAC) having molecular weights ranging from about 10,000 to 1,000,000. Amounts of DMDAAC homopolymer as low as 0.00001 percent by weight may be employed when an enhancer, such as thimerosal, sorbic acid or phenylmercuric salt is used therewith. Although lens binding and concomitant eye tissue irritation with DMDAAC were reduced, it was found in some users to be above desirable clinical levels.

British Patent 1,432,345 discloses contact lens disinfecting compositions containing a polymeric biguanide and a mixed phosphate buffer. The products embraced by this patent have not found acceptance by the consumer. Corneal staining is an indication of patient acceptability and compositions as disclosed by this patent have staining values of 17% or more present, far above that which is desirable for patient acceptability.

Other efforts to reduce or eliminate binding of disinfectants to contact lenses have led to the use of anti-binding or detoxifying agents, like polyvinyl pyrrolidone (PVP) and polyvinyl alcohol (PVA). For the most part, however, these polymers alone were found to be ineffective in reducing lens binding and eye tissue irritation.

U.S. Patent 4,758,595 to Ogunbiyi et al. disclosed that a contact-lens solution containing a polyaminopropyl biguanide (PAPB) has enhanced efficacy when combined with a borate buffer. Such solutions are compatible with both non-soft and soft-type lenses, and are adaptable for use with virtually any of the commonly known disinfecting techniques, including "cold" soaking under ambient temperature conditions, as well as with high temperature disinfecting methods. These disinfecting and preservative solutions are especially noteworthy for their broad spectrum of bactericidal and fungicidal activity at low concentrations coupled with very low toxicity when used with soft-type contact lenses. Ogunbiyi et al. stated that biguanide polymers in the higher molecular weight ranges usually demonstrate lower toxicity levels than corresponding lower molecular weight materials.

Compositions containing PAPB and borate, or other non-phosphate buffers, have been commercialized in various products, but at levels of about 1 ppm or less for use with soft contact lenses. It is generally desirable to provide the lowest level of a bactericide possible, while maintaining the desirable level of disinfection efficacy, in order to provide a generous margin for safety and comfort.

Some of the most popular products for disinfecting lenses are multipurpose solutions that can be used to clean, disinfect and wet contact lenses, followed by direct insertion (placement on the eye) without rinsing. Obviously, the ability to use a single solution for contact-lens care is an advantage. Such a solution, however, must be

particularly gentle to the eye, since, as indicated above, some of the solution will be on the lens when inserted and will come into contact with the eye.

With conventional contact-lens cleaners or disinfectants, including multi-purpose solutions, lens wearers typically need to digitally or manually rub the contact lenses (typically between a finger and palm or between fingers) during daily cleaning and/or disinfecting of contact lenses. The necessity for frequent "rubbing" of contact lenses adds to the time and effort involved in the daily care of contact lenses. Many contact-lens wearers dislike having to perform a daily "rubbing" regimen or consider it to be an inconvenience. Some wearers may be negligent in the proper "rubbing" regimen, which may result in contact-lens discomfort and other problems. Sometimes rubbing, if performed too rigorously, which is particularly apt to occur with beginning lens wearers, may damage the lenses. This can be very problematic or inconvenient when a replacement lens is not immediately available.

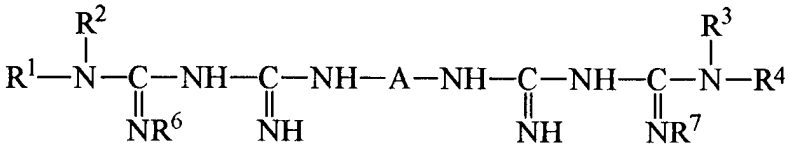
A contact lens solution that does not require rubbing would generally require a more efficacious or stronger disinfectant than a solution that does not require rubbing. The stronger the bactericidal effect of a solution, however, the more likely that it may exhibit toxic effects or adversely effect lens-wearer comfort. In fact, many very efficacious bactericides used in other contexts, such as mouthwashes, cosmetics, or shampoos, while being sufficiently safe for use in such products, would be too toxic for ophthalmic use, especially for use with soft lenses because of the above-mentioned tendency of soft lenses to bind chemicals. Similarly, the concentrations of certain bactericides may need to be within lower limits in solutions for use with soft contact lenses than in other products or in solutions for other types of lenses, especially when such solutions are for use in the eye.

It would be desirable to obtain a contact-lens solution that would simultaneously provide both (1) an increased level of antibacterial activity, and (2) a low order of toxicity to eye tissue, such that the solution can be used to treat contact lenses without rinsing, despite any tendency of a disinfectant to bind onto lens surfaces. While challenging to develop, it would be especially desirable to obtain such a disinfecting solution that could be used as a multi-purpose solution for soft contact lenses, which would allow direct

placement of a contact lens on an eye following soaking in the solution and/or rinsing and rewetting with the solution. Finally, it would be additionally desirable for the antibacterial efficacy of the disinfecting solution to be sufficiently high that rubbing would not be required to achieve effectively complete disinfection of a contact lens.

Brief Description of the Invention

The present invention is directed to an ophthalmically safe disinfecting solution for contact lenses comprising about 2.0 to about 8.0 ppm of a bis(biguanide) in the form of a dihydrochloride salt, or a corresponding concentration of the same bis(biguanide) in the form of the free base or a different water-soluble salt, which bis(biguanide) has the following general formula:



(I)

wherein R^1 and R^4 are independently selected (i.e., the same or different) from the group consisting of branched or unbranched alkyl having 4-12 carbon atoms, alkoxyalkyl or alkylsulfide radical having 4-12 carbon atoms, or cycloalkyl or cycloalkyl-alkyl radical having 5-12 carbon atoms; R^2 and R^3 are independently selected from the group consisting of hydrogen, alkyl having 1-12 carbon atoms, alkoxyalkyl having 1-12 carbon atoms, or cycloalkyl or cycloalkyl-alkyl having 5-12 carbon atoms; R^6 and R^7 are independently selected from the group consisting of hydrogen and alkyl radical having 1-6 carbon atoms, and A in the above formula is a divalent group having 4-16 carbon atoms and is selected from the group consisting of an alkylene, alkyloxyalkyl, and alkylsufide radical, wherein the aforesaid alkyoxyalkyl or alkylsulfide radicals are either a polymethylene chain interrupted with one or more oxygen and/or sulfur atoms or a polymethylene chain substituted with an alkoxy (-OR^8) or alkylthio (-SR^9) group, wherein R^8 and R^9 are independently selected from the group consisting of alkyl having 1-12 carbon atoms or a cycloalkyl or cycloalkyl-alkyl having 5-12 carbons, or wherein A is a

divalent polymethylene group having 8 to 16 carbon atoms interrupted with a divalent radical of cyclohexane or 1,4-diazacyclohexane.

The solutions of the present invention also comprise an effective amount of one or more buffering agents, preferably in the amount of from about 0.01 to 5% by weight of the composition (solution), an effective amount of one or more surfactants, preferably in an amount of about 0.01% to 5% by weight, and water in an amount of at least about 90% by weight. In one embodiment of the invention, the surfactant is a neutral or non-ionic surfactant.

The invention is also directed to a method of cleaning and/or disinfecting a contact lens comprising soaking the lens for a given period of time in an aqueous solution comprising a microbiocidally effective amount, within the range from about 2.0 to about 8.0 ppm, preferably 2.0 to 6.0 ppm, of a bis(biguanide) of Formula (I) in the form of the hydrochloride salt (or a corresponding concentration or molar amount of the same bis(biguanide) in the form of the free base or a salt other than the hydrochloride), an effective amount of a buffering agent, and an effective amount of a surfactant, and subsequently directly placing the treated lens on an eye of the wearer. In a preferred embodiment of this method, the contact lens does not require rubbing with the solution to achieve the necessary disinfection.

In yet another embodiment of the present invention, 0.1 to 4.0 ppm of a bis(biguanide) of Formula (I) has been shown to provide synergistic efficacy in combination with a polymeric biguanide in the amount of 0.1 to 3.0 ppm.

Detailed Description of the Invention

As indicated above, the present invention is directed to a composition, in the form of an aqueous solution containing a compound of Formula (I) above, and a method of using the solution for disinfecting and/or preserving contact lenses, especially soft contact lenses. The disinfecting solutions of the present invention are effective at low concentrations against a wide spectrum of microorganisms, including but not limited to *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Candida albicans*, and *Fusarium solani*. A disinfecting solution is generally defined as a contact-

lens care product containing one or more active ingredients (for example, anti-microbial agents and/or preservatives) in sufficient concentrations to destroy harmful microorganisms on the surface of a contact lens within the recommended minimum soaking time. The recommended minimum soaking time is included in the package instructions for use of the disinfecting solution. The present solution, in combination with its container or bottle and packaging, including instructions for use in accordance with a specified regimen, may be considered a novel and improved kit, package, or system for the care of contact lenses.

By the term "soft lens" is meant a lens having a proportion of hydrophilic repeat units such that the water content of the lens during use is at least 20% by weight. The term "soft contact lens" as used herein generally refers to those contact lenses which readily flex under small amounts of force. Typically, soft contact lenses are formulated from polymers having a certain proportion of repeat units derived from hydroxyethyl methacrylate and/or other hydrophilic monomers, typically crosslinked with a crosslinking agent. In contrast, conventional "hard contact lenses", which cover only a part of the cornea of the eye, usually consist of poly(methyl methacrylate) crosslinked with ethylene glycol dimethacrylate or the like, and conventional rigid gas permeable lenses (RGP) typically comprises monomers containing silicon that result in a more oxygen-permeable material.

By the term "disinfecting solution" is meant a solution containing one or more microbiocidal compounds, that is effective for reducing or substantially eliminating the presence of an array of microorganisms present on a contact lens, which can be tested by challenging the solution, or a contact lens that has been immersed in the solution, with specified inoculums of such microorganisms. The term "disinfecting solution" does not exclude the possibility that the solution may also be useful as a preserving solution, or that the disinfecting solution may also be useful for other purposes such as daily cleaning, rinsing and storage of contact lenses, depending on the particular formulation.

A solution that is useful for cleaning, chemical disinfection, storing, and rinsing a contact lens is referred to herein as a "multi-purpose solution." Such solutions may be part of a "multi-purpose solution system" or "multi-purpose solution package." The

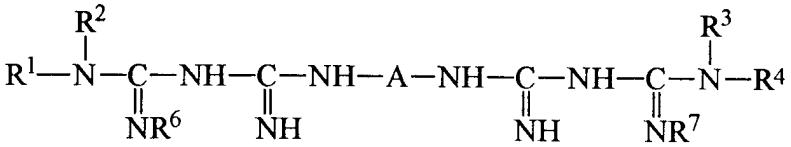
procedure for using a multi-purpose solution, system or package is referred to as a "multi-functional disinfection regimen." Multi-purpose solutions do not exclude the possibility that some wearers, for example, wearers particularly sensitive to chemical disinfectants or other chemical agents, may prefer to rinse or wet a contact lens with another solution, for example, a sterile saline solution prior to insertion of the lens. The term "multi-purpose solution" also does not exclude the possibility of periodic cleaners not used on a daily basis or supplemental cleaners for removing proteins, for example enzyme cleaners, which are typically used on a weekly basis. By the term "cleaning" is meant that the solution contains one or more cleaning agents in sufficient concentrations to loosen and remove loosely held lens deposits and other contaminants on the surface of a contact lens, especially if used in conjunction with digital manipulation (for example, manual rubbing of the lens with a solution) or with an accessory device that agitates the solution in contact with the lens, for example, a mechanical cleaning aid. The critical micelle concentration of a surfactant-containing solution is one way to evaluate its cleaning effectiveness.

The term "effective multi-purpose solution," "effective multi-purpose solution system," "effective multi-purpose solution package" and "effective multi-functional disinfection regimen" analogously refers to a solution useful for daily chemical disinfection, storing, and rinsing a contact lens, which solution does not require cleaning that involves rubbing, but which solution still obviates the need for any other solution for daily cleaning, that is, no other solution must be used in conjunction or combination with the solution on a daily basis. Such solutions may comprise a surfactant or other agent for loosening or preventing lens deposits to some extent. Such a solution does not require digital rubbing or similar manual or mechanical means that provide a rubbing action (a means for providing pressure and friction along the surface of the lens) to remove deposits from a lens. A no-rub regimen may be especially applicable to a frequent replacement lens, a lens which is recommended for replacement after a limited number of days in the eye of the wearer, for example, after being worn about 30 days or less, preferably after being worn about 14 days or less.

By the term "ophthalmically safe" with respect to a contact-lens solution is meant that a contact lens treated with the solution is safe for direct placement on the eye without

rinsing, that is, the solution is safe and comfortable for daily contact with the eye via a contact lens that has been wetted with the solution. An ophthalmically safe solution has a tonicity and pH that is compatible with the eye and comprises materials, and amounts thereof, that are non-cytotoxic according to ISO standards and U.S. FDA (Food & Drug Administration) regulations.

According to the present invention, the bis(biguanide) germicides employed in the present solutions include compounds, and their water-soluble salts, having following formula:



(I)

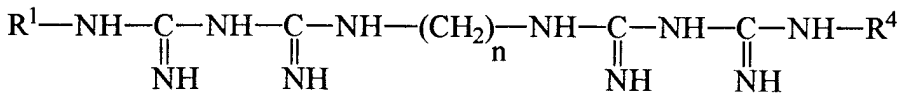
wherein R^1 and R^4 are independently selected (i.e., the same or different) from the group consisting of branched or unbranched alkyl having 4-12, preferably 6-10, carbon atoms, alkoxyalkyl (i.e., ether) or alkylsulfide (thioether or dialkylsulfide) radical having 4-12, preferably 6-10, carbon atoms, or cycloalkyl or cycloalkyl-alkyl radical having 5-12, preferably 7-10, carbon atoms; R^2 and R^3 are independently selected from the group consisting of hydrogen, alkyl having 1-12, preferably 1-6, carbon atoms, alkoxyalkyl having 1-12, preferably 1-6, carbon atoms, or cycloalkyl or cycloalkyl-alkyl having 5-12, preferably 6-10, carbon atoms; R^6 and R^7 are independently selected from the group consisting of hydrogen and alkyl radical having 1-6 carbon atoms, and A in the above formula is a divalent group having 4-16 carbon atoms, preferably 6-10, carbon atoms and is selected from the group consisting of an alkylene (a divalent radical of an aliphatic hydrocarbon), alkyloxyalkyl, and alkylsufide radical, wherein the aforesaid alkyoxyalkyl or alkylsulfide radicals are either a polymethylene chain interrupted with one or more oxygen and/or sulfur atoms or a polymethylene chain substituted with an alkoxy ($-OR^8$) or alkylsulfide ($-SR^9$) group, wherein R^8 and R^9 are independently selected from the group consisting of alkyl having 1-12 carbon atoms, or a cycloalkyl or cycloalkyl-alkyl having 5-12 carbon, or wherein A is a divalent polymethylene group having 8 to 16 carbon atoms, preferably 6 to 12 carbon atoms interrupted with a divalent radical of a cyclohexane or

diazacyclohexane ring (a 1,4-diazacyclohexane or piperazine connected to the polymethylene ring via the nitrogen atoms). By the term "cycloalkyl," either in cycloalkyl or cycloalkyl-alkyl, is meant unsubstituted or substituted cycloalkyl, where the substituents are one or more alkyl, alkoxy (-OR) , or alkylthio (-SR) groups having 1-6 carbon atoms.

In one embodiment of the present invention, the biguanides of Formula (I) are suitably used in the total amount (with respect to the weight of the hydrochloride salt, often containing two hydrochlorides as in alexidine) of 2.0 to 8.0 ppm, preferably 2.5 to 6.0 ppm based on the total aqueous solution. More preferably, the bis(biguanides) are used in the amount of 3.0 to 5.0, most preferably 3.5 to 4.5 ppm, with respect to the hydrochloride salt, or a corresponding molar amount of another salt or its free base. When the bis(biguanide) that is used in the present invention is in the form of the free base or a salt other than the hydrochloride, then the above-indicated ppm ranges must be adjusted to obtain the corresponding ppm ranges such that the ranges are the same on a molar basis as for the hydrochloride salt of the bis(biguanide). The concentration of the bis(biguanide) in solution is directly related to its bactericidal efficacy. The corresponding weight of an equal molar amount or equal concentration of a different salt form of a bis(biguanide) can be readily calculated, for use determining a suitable amount of the ingredient. The term "ppm" refers to "parts per million" and 1.0 ppm corresponds to 0.0001 percent by weight. It is based on the total weight of the composition or, in this case, the total weight of the aqueous disinfecting solution.

In the present application, the amount of the bis(biguanide) or other components in a solution according to the present invention refers to the amount formulated and introduced into the solution at the time the solution is made. Over time (for example, over a storage period of 18 months), the assayed amount of a bis(biguanide) in solution may decrease somewhat.

Preferably, the bis(biguanide) compounds have the following formula:



(II)

or their water-soluble salt form, wherein R^1 and R^4 are independently selected from the group consisting of branched or unbranched alkyl, alkoxyalkyl (i.e., ether) or alkylsulfide (thioether) radical, and n is 5 to 7.

Each of R^1 and R^4 in Formulas (I) or (II) above may be, for example, an n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl, octyl, 2-ethylhexyl, dodecyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentylmethyl or cyclohexylmethyl radical. Preferred are 2-ethylhexyl (alexidine), 1,5-dimethylhexyl, 1-methylhexyl, 1,3-dimethylpentyl, 1,4-dimethylpentyl, cyclohexylmethyl, 2-norbornyl, propyloxyoctyl, and propyloxybutyl.

Each of R^2 and R^3 in Formula (I) above may be, for example, a methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, neopentyl, octyl, 2-ethylhexyl, dodecyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentylmethyl or cyclohexylmethyl radical. When one or more of R^2 and R^3 is an alkoxyalkyl radical, it may be, for example, a 2-methoxyethyl.

Each of R^6 and R^7 in Formula (I) may be, for example, a methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, or neopentyl radical.

Preferred A groups in Formula (I) include hexamethylene and a divalent hexamethylene interrupted with a divalent radical derived from N,N'-(2-aminoethyl)-1,4-piperadine or the like in which each of the nitrogen atoms are connected to a polymethylene group having 1 to 4 carbon atoms.

The acid-addition salts of the invention may be derived from an inorganic or organic acid. In most circumstances it is preferable that the salts be derived from an acid which is readily water soluble and which affords an anion which is suitable for human usage, for example a pharmaceutically-acceptable anion. Examples of such acids are hydrochloric, hydrobromic, phosphoric, sulphuric, acetic, D-gluconic, 2-pyrrolidino-5-carboxylic, methanesulphonic, carbonic, lactic and glutamic acids. The hydrochloride salt is preferred.

The bis(biguanides) of Formula (I) preferably have relatively hydrophobic end groups. Preferably, the Log P of the compounds is 5 to 10, preferably 6 to 8, wherein P

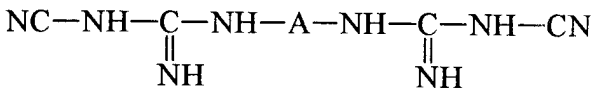
is the partition coefficient of the free base, using the following equation, wherein α is the degree of ionization:

$$P = \frac{C_{octanol}}{C_{buffer}(1-\alpha)}$$

To obtain the partition coefficient of a bis(biguanide), the compound is partitioned between a 0.05 M phosphate buffer (pH 11) saturated with octanol and octanol saturated with phosphate buffer after gentle shaking at room temperature (26 °C). The volume ratio of these two phases and the amount of sample are chosen so that the absorbance of the sample from the buffered layer after partitioning has a value between 0.2 and 0.9, using a 1-cm cell and buffer solution as a blank. By working at a fixed pH and knowing or calculating the pK_a, the P value can be determined using the above formula. See "Quantitative Structure-Activity Relationships for Biguanides, Carbamidates, and Bisbiguanides as Inhibitors of Streptococcus mutans NO. 6715", and Warner, V. and Lynch, D., *J. Med. Chem*, 1979, Vol. 22, no. 4 at 359, 365; and Albert, and Serjeant, E., "Determination of Ionization and Stability Constants," Butler and Tanner Ltd., London, England, 1962, both references hereby incorporated by reference.

Particularly preferred bis(biguanide) compounds of this invention are 2-(decylthiomethyl)-pentane-1,5-bis(5-isopropylbiguanide), 2-(decylthio-methyl)pentane-1,5-bis(5,5-diethylbiguanide), and hexane-1,6-bis(2-ethylhexylbiguanide), the latter also known as alexidine or 1,1'-hexamethylenebis(5-(2-ethylhexyl)-biguanide) dihydrochloride. Other preferred bis(biguanides) include 1,1'-hexamethylenebis(5-heptyl-biguanide) dihydrochloride, 1,1'-hexamethylenebis(5-octyl-biguanide) dihydrochloride, and 1,1'-hexamethylenebis(5-hexyl-biguanide) dihydrochloride.

The biguanide compounds of Formula (I) wherein R^6 and R^7 are each hydrogen may be made by reacting a bis-cyanoguanidine of the formula:



(VI)

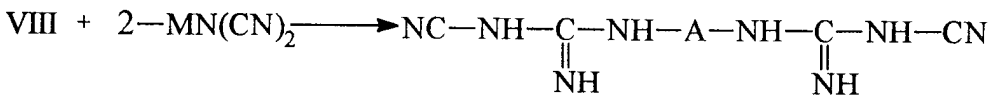
with an amine R^1R^2NH, or with two different amines R^1R^2NH and R^3R^4NH, in the form of an acid addition salt thereof, wherein A, R^1, R^2, R^3 and R^4 have the meanings stated

above, at a temperature of 100°C to 170°C. A preferred amine salt is the hydrochloride. Most diamines are commercially available from a variety of sources.

The reactants are heated together until the reaction is complete. The reaction proceeds fastest at higher temperatures, but if thermal stability is a problem, the reaction should be carried out at lower temperature for a longer period. The reactants are most conveniently melted together in the absence of a solvent, but if desired an inert solvent such as DMSO, 2-methoxyethanol, 2-ethoxyethanol, nitrobenzene, sulpholane, isopropanol, n-butanol, ethylene glycol dimethyl ether or water, or a mixture of such solvents, may be used.

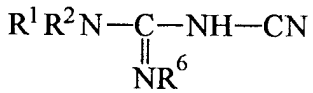
The bis-cyanoguanidine of the Formula (VI) may be manufactured from known starting materials such as hexamethylenedinitrile which is reduced, for example, with hydrogen and Raney nickel or with borane in dimethyl sulphide to the corresponding diamine (VIII), and the diamine in the form of an acid-addition salt, conveniently the dihydrochloride, is reacted with sodium dicyanamide or other suitable salt to form the required starting material (VI), as depicted below.

(VII) (VIII)



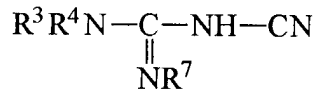
wherein M is a sodium, potassium, zinc or other suitable salt. The sodium salt is commercially available.

The compounds of the present invention can also be made by reacting a diamine of the Formula (VIII) in the form of an acid addition salt, with a cyanoguanidine of the formula:



(IX)

or with a cyanoguanidine of the Formula (IX) and a cyanoguanidine of the formula:



(X)

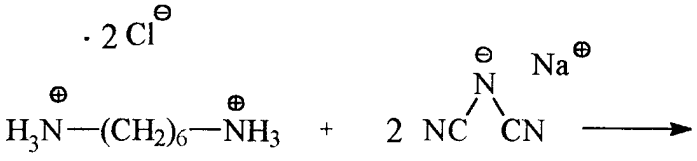
wherein A, R^1, R^2, R^3, R^4, R^6 and R^7 have the meanings stated above, at a temperature of 100° to 170°C.

A suitable salt of the diamine is, for example, the dihydrochloride. The reactants are heated together until the reaction is complete. The reaction proceeds fastest at higher temperature, but if thermal stability is a problem, the reaction should be carried out at lower temperature over a longer period. If a melt can be formed at those temperatures the reactants are conveniently melted together in the absence of a solvent. If not, or alternatively, the reactants are heated together in a suitable inert solvent, for example those mentioned above. The acid-addition salts of the invention are obtained by conventional means.

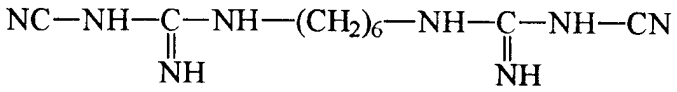
The cyanoguanidines of the Formulae (IX) and (X) wherein R^6 and R^7 are hydrogen, which may be used as starting materials in the above process, may be obtained by reacting sodium dicyanamide with an appropriate amine R^1R^2NH or R^3R^4NH, in the form of an acid-addition salt, conveniently the dihydrochloride, in a suitable inert solvent.

The cyanoguanidines of the Formulae (IX) and (X) wherein R^6 and R^7 are other than hydrogen, which may be used as starting materials in the above process, may be obtained by reacting a dialkyl (cyanoimido)dithio-carbonate, for example dimethyl (cyanoimido)dithio-carbonate, with appropriate amines R^1R^2NH and R^6NH_2 or R^3R^4NH and R^7NH_2.

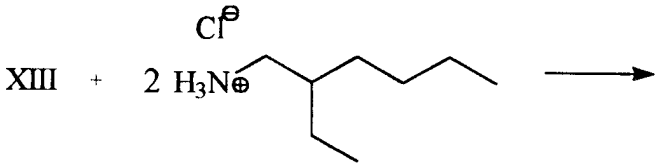
For example, the bis(biguanide) known as alexidine is produced from the following sequence of reactions.



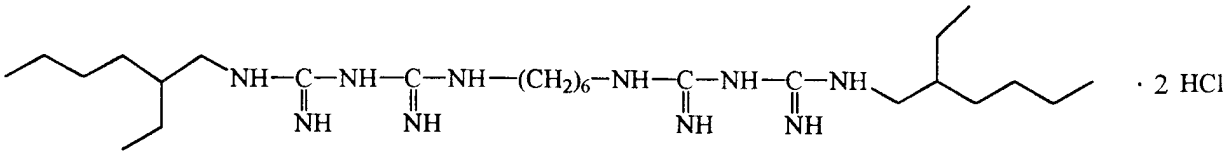
(XI) (XII)



(XIII)



(XIV)



(XV)

Compound (XI) is hexamethylenediamine dihydrochloride (MW 189), Compound (XII) is sodium dicyanamide, Compound XIII is HMBDA, hexamethylene bis(cyanoguanido), Compound (XIV) is 2-ethyl-hexylamine hydrochloride (MW 165.7), and Compound (XV) is alexidine dihydrochloride a.k.a. [1,6-bis-(2-ethylhexylbiguanido]hexane dihydrochloride a.k.a. hexane-1,6-bis(2-ethylhexyl biguanide) dihydrochloride. This compound has a molecular weight in g/mole (MW) of 581.7 and empirical formula $C_{26}H_{56}N_{10}\cdot 2HCl$. The Compound (XV) is commercially available from various sources, including Sigma Chemical Co. (St Louis, Missouri).

Various compounds can be made by appropriate starting materials, for example, where "A" in Formula (I) above is an alkoxy or thioalkyl-substituted alkylene, a compound of Formula (VII) may be made from hexenedinitrile by reaction with R^5YH, where Y is an oxygen or sulfur atom as a strong base. Various compounds of Formula (I), where R^2 and R^3 are H, can be readily obtained as N derivatives of 1,6-bis(biguanido)hexane.

The methods for synthesized compounds of the present invention are also disclosed in European Patent Application Publication No. 0 125 092 (published 14.11.84); Rose, F.L. and Swain, G., "Bisdiguanide Having Antibacterial Activity," *J. Chem. Soc.*, p. 4422-4425 (1956); Warner, Victor D. and Lynch, Donald, "Quantitative Structure-Activity Relationships of Biguanide, Carbamimidates, and Bisdiguanides as Inhibitors of Streptococcus Mutans No. 6715," *J. Med. Chem.*, Vol. 22, No. 6, p. 359-366 (1979).

A second disinfectant/germicide can be employed as a solution preservative, but it may also function to potentiate, compliment or broaden the spectrum of microbiocidal activity of Formula (I). This includes microbiocidally effective amounts of germicides which are compatible with and do not precipitate in the solution, in concentrations ranging from about 0.00001 to about 0.5 weight percent, and more preferably, from about 0.0001 to about 0.1 weight percent. Suitable complementary germicidal agents include, but are not limited to thimerosol, sorbic acid, alkyl triethanolamines, phenylmercuric salts, e.g. nitrate, borate, acetate, chloride and mixtures thereof. Suitable salts are soluble in water at ambient temperature to the extent of at least 0.5 weight percent. These salts include the gluconate, isethionate, (2-hydroxyethanesulfonate), formate, acetate, glutamate, succinanate, monodiglycollate, methanesulfonate, lactate, isobutyrate and glucoheptonate.

Further embodiments of potentiating or complementary disinfecting agents for use in the present invention also include certain quaternary ammonium compounds which possess a generally wide spectrum of bacteriocidal activity and wetting properties. Representative examples of the quaternary ammonium compounds are compositions comprised of balanced mixtures of n-alkyl dimethyl benzyl ammonium chlorides. Other examples include polymeric quaternary ammonium salts used in ophthalmic applications such as polyquaternium 1® (chemical registry number 75345-27-6) available from Onyx corporation.

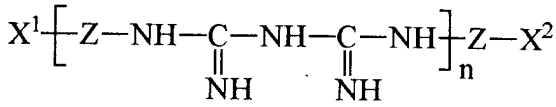
In another embodiment of the present invention, the bis(biguanides) defined above may be used in combination with lesser amounts of other bis(biguanides), for example

chlorhexidine. Such compounds have been disclosed in greater detail in United Kingdom patent specification No. 705,838.

Finally, the bis(biguanides) of the present invention (Formula I or II) may be used in combination with one or more polymeric biguanides. In particular, one embodiment of the present invention is directed to an ophthalmically safe disinfecting solution for contact lenses comprising: about 0.10 to about 4.0 ppm of a bis(biguanide), as defined herein, in combination with 0.10 to 3.0 ppm of a polymeric biguanide. Preferably, the bisbiguanide has Formula (II) provided above, wherein R^1 and R^4 are independently selected from the group consisting of branched or unbranched alkyl having 4-12, preferably 6-10, carbon atoms, alkoxyalkylor alkylsulfide radical having 4-12, preferably 6-10, carbon atoms, or cycloalkyl or cycloalkyl-alkyl radical having 5-12, preferably 7-10, carbon atoms; and n is 4 to 16, preferably 4 to 10.

In this embodiment, in which a bis(biguanide) is used in a synergistic combination with a polymeric biguanide, the bis(biguanides) of Formula (I) are suitably used (with respect to the weight of the hydrochloride salt, often containing two hydrochlorides as in alexidine) in the amount of 0.1 to 4.0 ppm, preferably 1.0 to 3.0 ppm based on the total aqueous solution. More preferably, the bis(biguanides) are used in the amount of 1.5 to 2.5, most preferably about 2.0 ppm, with respect to the hydrochloride salt, or a corresponding molar amount of another salt or its free base. When the bis(biguanide) that is used in the present invention is in the form of the free base or a salt other than the hydrochloride, then the above-indicated ppm ranges must be adjusted to obtain the corresponding ppm ranges such that the ranges are the same on a molar basis as for the hydrochloride salt of the bis(biguanide).

In this embodiment, 0.10 to 4.0 ppm of the bis(biguanides) of the present invention (Formula I or II) may be used in combination with one or more polymeric biguanides, and water-soluble salts thereof, having the following formula:



(IV)

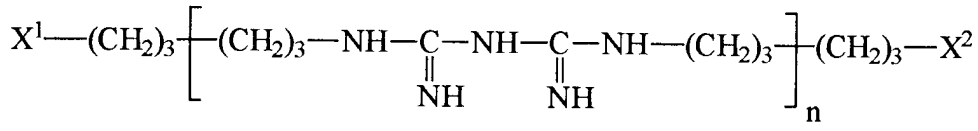
wherein Z is an organic divalent bridging group which may be the same or different throughout the polymer, n is on average at least 3, preferably on average 5 to 20, and X^1 and X^2 are independently selected from the groups $-NH_2$ and -NH - C - NH - CN. (NH)

One preferred group of water-soluble polymeric biguanides will have number average molecular weights of at least 1,000 and more preferably will have number average molecular weights from 1,000 to 50,000. Suitable water-soluble salts of the free bases include, but are not limited to hydrochloride, borate, acetate, gluconate, sulfonate, tartrate and citrate salts.

The above-disclosed biguanides and methods of preparation are described in the literature. For example, U.S. patent 3,428,576 describes the preparation of polymeric biguanides from a diamine and salts thereof and a diamine salt of dicyanimide.

The polymeric biguanides, in combination with the bisbiguanides of the present invention, are effective in concentrations as low as 0.00001 weight percent (0.1 ppm). It has also been found that the bactericidal activity of the solutions may be enhanced or the spectrum of activity broadened through the use of a combination of such polymeric biguanides with the compounds of Formula (I) above. The effective amount of the polymeric biguanides (irrespective of the particular salt form or whether the free base is used) may in total be as low as about 0.000010 weight percent (0.10 ppm) and up to about 0.00030 weight percent (3.0 ppm) in the present invention, whether in the form of a water-soluble salt or the free base. Preferably, the total amount of polymeric biguanide, in combination with the total amount of compounds of Formula (I) above is about 0.3 to 2.0 ppm, more preferably about 0.4 to 1.0, most preferably about 0.5 to 0.8 ppm.

Most preferred are the polymeric hexamethylene biguanides, commercially available, for example, as the hydrochloride salt from Zeneca (Wilmington, DE) under the trademark Cosmocil™ CQ. Such polymers and water-soluble salts are referred to as PHMB or polyaminopropyl biguanide (PAPB). The term polyhexamethylene biguanide, as used herein, is meant to encompass one or more biguanides have the following formula:



(V)

wherein X^1 and X^2 are as defined above and n is from 1 to 500.

Depending on the manner in which the biguanides are prepared, the predominant compound falling within the above formula may have different X^1 and X^2 groups or the same groups, with lesser amounts of other compounds within the formula. Such compounds are known and are disclosed in US Patent No. 4,758,595 and British Patent 1,432,345, which patents are hereby incorporated herein by reference. Preferably, the water-soluble salts are compounds where n has an average value of 2 to 15, most preferably 3 to 12.

The present solution comprises at least one surfactant. Suitable surfactants can be either amphoteric, cationic, anionic, or nonionic which may be present (individually or in combination) in amounts up to 15 percent, preferably up to 5 percent by weight of the composition or solution. Preferred surfactants are amphoteric or nonionic surfactants, which when used impart cleaning and conditioning properties. The surfactant should be soluble in the lens care solution and non-irritating to eye tissues. Many nonionic surfactants comprise one or more chains or polymeric components having oxyalkylene (-O-R-) repeats units wherein R has 2 to 6 carbon atoms. Preferred non-ionic surfactants comprise block polymers of two or more different kinds of oxyalkylene repeat units, which ratio of different repeat units determined the HLB of the surfactant. Satisfactory non-ionic surfactants include polyethylene glycol esters of fatty acids, e.g. coconut, polysorbate, polyoxyethylene or polyoxypropylene ethers of higher alkanes (C_{12}-C_{18}). Examples of the preferred class include polysorbate 20 (available under the trademark Tween® 20), polyoxyethylene (23) lauryl ether (Brij® 35), polyoxyethyene (40) stearate (Myrj® 52), polyoxyethylene (25) propylene glycol stearate (Atlas® G 2612). One non-ionic surfactant in particular consisting of a poly(oxypropylene)-poly(oxyethylene) adduct of ethylene diamine having a molecular weight from about 7,500 to about 27,000 wherein at least 40 weight percent of said adduct is poly(oxyethylene) has been found to be particularly advantageous for use in cleaning and conditioning both soft and hard contact

lenses when used in amounts from about 0.01 to about 15 weight percent. The CTFA Cosmetic Ingredient Dictionary's adopted name for this group of surfactants is poloxamine. Such surfactants are available from BASF Wyandotte Corp., Wyandotte, Michigan, under the registered trademark "Tetronic". An analogous of series of surfactants, suitable for use in the present invention, is the poloxamer series which is a poly(oxyethylene) poly(oxypropylene) block polymers available under the trademark "Pluronic" (commercially available form BASF).

Various other ionic as well as amphoteric and anionic surfactants suitable for in the invention can be readily ascertained, in view of the foregoing description, from McCutcheon's Detergents and Emulsifiers, North American Edition, McCutcheon Division, MC Publishing Co., Glen Rock, NJ 07452 and the CTFA International Cosmetic Ingredient Handbook, Published by The Cosmetic, Toiletry, and Fragrance Association, Washington, D.C.

Amphoteric surfactants suitable for use in a composition according to the present invention include materials of the type are offered commercially under the trade name "Miranol." Another useful class of amphoteric surfactants is exemplified by cocoamidopropyl betaine, commercially available from various sources.

The foregoing surfactants when employed with a buffer enhancer will generally be present in an amount from 0.01 to 5.0 percent (w/w), preferably 1.0 to 5.0 percent.

Typically, the aqueous solutions of the present invention for treating contact lenses are also adjusted with tonicity agents, to approximate the osmotic pressure of normal lacrimal fluids which is equivalent to a 0.9 percent solution of sodium chloride or 2.5 percent of glycerol solution. The solutions are made substantially isotonic with physiological saline used alone or in combination, otherwise if simply blended with sterile water and made hypotonic or made hypertonic the lenses will lose their desirable optical parameters. Correspondingly, excess saline may result in the formation of a hypertonic solution which will cause stinging and eye irritation.

The pH of the present solutions should be maintained within the range of 5.0 to 8.0, more preferably about 6.0 to 8.0, most preferably about 6.5 to 7.8, suitable buffers may be added, such as boric acid, sodium borate, potassium citrate, citric acid, sodium

bicarbonate, TRIS, and various mixed phosphate buffers (including combinations of Na_2HPO_4, NaH_2PO_4 and KH_2PO_4) and mixtures thereof. Borate buffers are preferred, particularly for enhancing the efficacy of biguanides. Generally, buffers will be used in amounts ranging from about 0.05 to 2.5 percent by weight, and preferably, from 0.1 to 1.5 percent. The disinfecting/preserving solutions of this invention preferably contain a borate or mixed phosphate buffer, containing one or more of boric acid, sodium borate, potassium tetraborate, potassium metaborate or mixtures of the same. In addition to buffering agents, in some instances it may be desirable to include sequestering agents in the present solutions in order to bind metal ions which might otherwise react with the lens and/or protein deposits and collect on the lens. Ethylene-diaminetetraacetic acid (EDTA) and its salts (disodium) are preferred examples. They are usually added in amounts ranging from about 0.01 to about 0.2 weight percent. Other suitable sequestering agents include gluconic acid, citric acid, tartaric acid and their salts, e.g. sodium salts.

The aqueous isotonic solutions of the bis(biguanides) of Formula (I) with optional other germicidal agents are especially useful for soft contact lenses, with or without further additives. Nevertheless, the solutions of the present invention may be formulated into specific contact lens care products, such as wetting solutions, soaking solutions, cleaning and conditioning solutions, as well as multi-purpose type lens care solutions, etc. and mixtures thereof. Such additives make the solutions more acceptable to the user in terms of greater comfort. However, the additives must be non-toxic and compatible with contact lenses.

It may also be desirable to include water-soluble viscosity builders in the solutions of the present invention. Because of their demulcent effect, viscosity builders have a tendency to enhance the lens wearer's comfort by means of a film on the lens surface cushioning impact against the eye. Included among the water-soluble viscosity builders are the cellulose polymers like hydroxyethyl or hydroxypropyl cellulose, carboxymethyl cellulose and the like. Such viscosity builders may be employed in amounts ranging from about 0.01 to about 4.0 weight percent or less. The present solutions may also include optional demulcents.

The aqueous solutions according to the present invention can be effectively used in disinfecting contact lenses by any of the well recognized methods. The lenses may be treated by the "cold" soaking method at room temperature for a period ranging from about 20 minutes to about 12 hours. The lenses are then removed from the solution, rinsed with the same or a different solution, for example a preserved isotonic saline solution and then replaced on the eye.

As indicated above, contact-lens wearers are commonly required to digitally or manually rub the contact lenses (typically between a finger and palm or between fingers) during daily cleaning and/or disinfecting of contact lenses. In one embodiment of the present invention, a method is provided in which rubbing is not required during treatment with the claimed specified solution, between removal from the eye and replacement of the lens following lens care. In a preferred embodiment of such a method, a soft lens is disinfected or both disinfected and cleaned with a multipurpose solution or an effective multipurpose solution that is the only daily solution needed for treating the lens outside the eye. Thus, in one embodiment of a method according to the invention, the described solution is used to treat a contact lens without rubbing, by a method comprising:

(a) soaking the contact lens that has not been rubbed with the solution for a specified time period, and

(b) direct placement of the treated contact lens on the eye of the wearer.

Typically, step (a) may involve immersing the contact lens in the solution. Soaking may optionally comprise shaking or similarly agitating a container of the solution by manual means. Preferably, step (a) involves a period of soaking the contact lens in a container wherein the contact lens is completely immersed in the solution. By the term "direct placement" is herein meant that the solution is not diluted or rinsed off the lens with a different contact-lens solution prior to "insertion" or placement on the eye. In a particularly preferred embodiment, the method uses a no-rub multi-purpose or effective multi-purpose solution, wherein no other solution or product is required for daily cleaning of the lens, with the possible exception of an enzyme cleaner.

Because of the increased microbial efficacy of the solution according to the present invention, the solution may be used to treat a lens, without rubbing the lens, in a regimen comprising a soak period that is less than four hours, for example, where sufficient disinfection can be obtained within a period that is in the range of about 20 minutes to about 90 minutes, wherein the recommended minimum soaking period is a given time within the range of about 20 minutes to about 90 minutes. Preferably, the solution may be formulated to provide the necessary disinfection, without rubbing, by soaking the lens in the solution for a given period within the range of about 50 minutes to about 70 minutes, preferably about 60 minutes, corresponding to a minimum soaking period of about 50 to about 70 minutes, preferably a minimum soaking period of about 60 minutes.

In yet another embodiment of a method according to the present invention, the claimed solution is used to clean a frequent replacement lens (FRL) that is planned for replacement after not more than about three months of use in the eye, or that is planned for replacement after not more than about 30 days of use in the eye, or that is planned for replacement after not more than about two weeks in the eye. Preferably, the lens is made from a polymer comprising about 0.0 to 5 mole percent repeat units derived from methacrylic acid (MAA), 10 to 99 mole percent of repeat units derived from hydroxyethyl methacrylate, and about 0.5 to 5 mole percent of cross-linking repeat units. Cross-linking repeat units may be derived, for example, from such monomers as ethyleneglycol dimethacrylate, divinylbenzene, and trimethylpropane trimethacrylate.

The following Examples illustrate the compositions and methods of the instant invention.

EXAMPLE 1

This Example illustrates the preparation of 1,6 bis(cyanoguanidino) hexane, used as a starting material for bis(biguanides) of the present invention. In the amount of 35.80 g (0.402 mole), sodium dicyanamide (NaC_2N_3) is suspended in 400 mL of 1-butanol. Then, 23.60 g (0.204 mole) of 1,6-hexanediamine were added as well as 33.0 mL of conc. aqueous hydrochloric acid (0.400 mole). A milky white precipitate appeared immediately

which was probably the amine hydrochloride. The mixture was then refluxed for 3.5 hr. The suspension was then cooled to room temperature and filtered. The white solid was then washed well with distilled water before drying under vacuum. Yield 46.38 g; 93.1%. C 10 H 18 N 8 calc'd: C 48.0%; H 7.20%; N 44.80%; found: C 47.7%; H 7.40%; N 45.12%. 300 MHz ^{1}H NMR (d^6-DMSO) 6.60 ppm (6p, br m); 2.93 ppm (4p, m); 1.34 ppm (4p, br s); 1.15 ppm (4p, br s). IR (KBr pellet, cm^{-1}) 3142 (m); 2943; 2912; 2862 (w); 2179 (s); 1658; 1609 (s).

EXAMPLE 2

This Example illustrates the preparation of alexidine for use in the present invention. Hexamethylene bis(cyanoguanido) in the amount of 1.003g (0.004498 moles) was placed into a flask. To this was added 1.474 mL (1.163g; 0.008996 moles) of 2-ethylhexylamine. Then, 0.74 mL (0.008996 moles) of concentrated HCl was added. The mixture was heated in a flask to boil away the H_2O. After the H_2O was gone, the temperature of the melt had risen to 195°C. The temperature was decreased to 150-160°C and maintained for 1 hour. The material was cooled to room temperature. The solid can be dissolved in hot water and allowed to crystallize.

EXAMPLE 3

This Example illustrates the preparation of poly(hexamethylene biguanide), also referred to as PAPB or PHMB, for use in combination with bis(biguanides) in the present invention. In 500 mL of distilled water was suspended 25.08 g (0.100 mole) of 1,6-bis(cyanoguanidino)hexane and 18.99 g (0.100 mole) of 1,6-hexanediamine dihydrochloride. The pH of this mixture was then brought down to 6.8 with dilute hydrochloric acid. The water was then removed by distillation under reduced pressure. The white solid was then transferred to a three-necked flask fitted with a mechanical stirrer and heating mantle. The intimate mixture of solids was then placed under nitrogen and the temperature of the mixture was raised to 150-55°C. The molten reaction mixture possessed the consistency of honey. The mixture was stirred at 150-55°C for 1 - 1.5 hr. before cooling to room temperature. The resulting poly(hexamethylene biguanide) is

obtained as a glassy solid. The yield is essentially quantitative. Melting range 105-125°C. 300 MHz ^{1}H NMR (D_2O) 3.13 ppm (21.1p, br t); 2.93 ppm (2p, t); 1.49 ppm (21.1p, br s); 1.28 ppm (21.1p, br s). IR (KBr pellet, cm^{-1}) 3325; 3201 (s); 2931; 2858 (m); 2175 (m-w); 1631; 1589; 1550(s).

EXAMPLE 4

This Example illustrates the preparation of an aqueous contact-lens disinfectant solution according to the present invention.

TABLE 1

	Percent (w/v)
Alexidine•2HCl	0.0004
Poloxamine 1107 **	1.0
Na_2EDTA	0.11
Boric Acid	0.66
Sodium Borate	0.10
Sodium Chloride	0.54
Distilled Water qs	100.0

** molecular weight 14,500, 70% (w/v) Tetronic® 1107, a poly(oxypropylene) poly(oxyethylene) block copolymer adduct of ethylene diamine, a trademark of BASF Wyandotte Corp., Wyandotte, MI.

The solution is prepared by gradually heating 80 percent of the water to 80°C while dissolving the disodium EDTA therein. The boric acid and sodium borate are added to the heated solution of disodium EDTA and dissolved. The sodium chloride is then added to the solution and dissolved, followed by the addition of surfactants. The solution is sterilized by autoclaving to 120°C for 45 minute. After the solution is cooled to room temperature, the bis(biguanide) is added through a sterile filter, followed by the balance of distilled water. The solution is packaged in sterilized plastic containers.

EXAMPLE 5

This Example illustrates the microbiocidal efficacy of solutions according to the present invention. The antimicrobial efficacy of each of various compositions for the chemical disinfection of contact lenses was evaluated. Microbial challenge inoculums were prepared using *Pseudomonas aeruginosa* (ATCC 9027), *Staphylococcus aureus* (ATCC 6538), *Serratia marcescens* (ATCC 13880), *Candida albicans* (ATCC 10231), and *Fusarium solani* (ATCC 36031). The test organisms were cultured on appropriate agar and the cultures were harvested using sterile DPBST (Dulbecco's Phosphate Buffered Saline plus 0.05% w/v polysorbate 80) or a suitable diluent and transferred to a suitable vessel. Spore suspensions were filtered through sterile glass wool to remove hyphal fragments. *Serratia marcescens*, as appropriate, was filtered (eg., through a 1.2μ filter) to clarify the suspension. After harvesting, the suspension was centrifuged at no more than 5000 x g for a maximum of 30 minutes at 20-25°C. The supernatant was poured off and resuspended in DPBST or other suitable diluent. The suspension was centrifuged a second time, and resuspended in DPBST or other suitable diluent. All challenge bacterial and fungal cell suspensions were adjusted with DPBST or other suitable diluent to 1 x 10^7-10^8 cfu/mL. The appropriate cell concentration may be estimated by measuring the turbidity of the suspension, for example using a spectrophotometer at a preselected wavelength, for example 490 nm. One tube was prepared containing a minimum of 10 mL of test solution per challenge organism. Each tube of the solution to be tested was inoculated with a suspension of the test organism sufficient to provide a final count of 1.0 x 10^5-10^6 cfu/mL, the volume of the inoculum not exceeding 1% of the sample volume. Dispersion of the inoculum was ensured by vortexing the sample for at least 15 seconds. The inoculated product was stored at 10-25°C. Aliquots in the amount of 1.0 mL were taken of the inoculated product for determination of viable counts after certain time periods of disinfection. The time points for the bacteria were, for example, 1, 2, 3, and 4 hours when the proposed regimen soaking time was 4 hours. Yeast and mold were tested at an additional timepoint of ≥ 16 hours (4 times the regimen time). The suspension was mixed well by vortexing vigorously for at least 5 second. The 1.0 mL aliquots removed at the specified time

intervals were subjected to a suitable series of decimal dilutions in validated neutralizing media. The suspensions were mixed vigorously and incubated for a suitable period of time to allow for neutralization of the microbial agent. The viable count of organisms was determined in appropriate dilutions by preparation of triplicate plates of trypticase soy (TSA) agar for bacteria and Sabouraud dextrose agar (SDA) for mold and yeast. The bacterial recovery plates were incubated at 30-35°C for 2-4 days. The yeast was incubated at 20-30°C for 2-4 days and mold recovery plates at 20-25°C for 3-7 days. The average number of colony forming units was determined on countable plates. Countable plates refer to 30-300 cfu/plates for bacteria and yeast, and 8 to 80 cfu/plate for mold except when colonies are observed only for the 10^0 or 10^{-1} dilution plates. The microbial reduction was then calculated at the specified time points. In order to demonstrate the suitability of the medium used for growth of the test organisms and to provide an estimation of the initial inoculum concentration, inoculum controls were made by dispersing an identical aliquot of the inoculum into a suitable diluent, for example DPBST, using the same volume of diluent used to suspend the organism as listed above. Following inoculation in a validated neutralizing broth and incubation for an appropriate period of time, the inoculum control must be between 1.0×10^5 - 1.0×10^6 cfu/mL

The solutions were evaluated based on the performance requirement referred to as the "Stand-Alone Procedure for Disinfecting Products" (hereafter the "stand-alone test") and is based on the Disinfection Efficacy Testing for contact lens care products under the Draft Premarket Notification (510(k)) Guidance Document For Contact Lens Care Products dated April 1, 1996, prepared by the U.S. Food and Drug Administration, Division of Ophthalmic Devices. This performance requirement is comparable to current ISO standards for disinfection of contact lenses (revised 1995). The stand-alone test challenges a disinfecting product with a standard inoculum of a representative range of microorganisms and establishes the extent of viability loss at pre-determined time intervals comparable with those during which the product may be used.. There is a primary performance criteria and secondary performance criteria. The primary criteria for a given disinfection period (corresponding to a potential minimum recommended disinfection period) is that the number of bacteria recovered per mL must be reduced by a mean value

of not less than 3.0 logs within the given disinfection period. The number of mold and yeast recovered per mL must be reduced by a mean value of not less than 1.0 log within the minimum recommended disinfection time with no increase at four times the minimum recommended disinfection time. If failing to pass this primary performance criteria, the secondary performance criteria exists which if passed qualifies the solution for the so-called "regimen test procedure" described in the FDA's Draft for Premarket Notification (510(k)) Guidance Document For Contact Lens Care Product, dated April 1, 1996 or similarly described in the ISO/CEN regimen test procedure. Under the secondary performance criteria, there must be a combined log reduction for the mean values of all three bacteria of not less than 5.0 logs within the recommended given disinfection period. The minimum acceptable mean log reduction for any single bacterial type is 1.0 log. Stasis for the yeast and mold must be observed for the recommended disinfection period. If passing the secondary performance criteria (also referred to as minimum antimicrobial activity by the Stand-Alone Procedure), the regimen test challenges the proposed disinfection regimen (typically involving rubbing) with a standard inoculum of a representative range of microorganisms, in which test the inoculum is carried through the various stages of regimen by preliminary application to contact lenses.

The above testing procedures were used for evaluating the antimicrobial efficacy of disinfecting solutions such as prepared in Example 4, but which contain the bis(biguanide) alexidine at various concentrations extending from 1 ppm to 5 ppm for a testing period of one hour. The results are shown in Table 2 below

TABLE 2

Microorganism	Alexidine•2HCl Concentration (ppm)	Log Reduction (1 hr)
S. aureus	1	1.6
S. aureus	2	4.3
S. aureus	3	>4.8
S. aureus	4	>4.8
S. aureus	5	>4.8
P. aeruginosa	1	>5.0
P. aeruginosa	2	>5.0
P. aeruginosa	3	>5.0
P. aeruginosa	4	>5.0
P. aeruginosa	5	>5.0
S. marcescens	1	3.5
S. marcescens	2	>4.8
S. marcescens	3	>4.8
S. marcescens	4	>4.8
S. marcescens	5	>4.8

The above results show that at 2.0 ppm the bis(biguanide) alexidine solution passes the one hour stand-alone test for bacteria, by which a 3 log reduction of all three bacteria is needed in the given disinfection time. According to the above results, at 1.0 ppm, alexidine will not pass the one hour stand-alone test for bacteria (failing with respect to *Serratia marcescens*). In order to pass the 1 hour stand-alone test, the fungi must also be tested, as in the next example.

EXAMPLE 6

This Example shows the antimicrobial efficacy of the solution of Example 4 according to the present invention using the testing procedures described in Example 5 above, but formulated at a concentration of 4.0 ppm alexidine and at time intervals of 15

minutes, 30 minutes, 45 minutes, and 60 minutes, which would represent 25%, 50%, 75% and 100% of a one hour minimum recommended disinfection time. The solution had been aged for 19 months at 25°C. The results are shown in Table 3 below.

TABLE 3

Microorganism	Soak Period	Log Reduction
Staphylococcus aureus	15 min.	2.5
	30 min.	4.4
	45 min.	>4.9
	60 min.	>4.9
Pseudomonas aeruginosa	15 min.	4.0
	30 min.	>4.8
	45 min.	>4.8
	60 min.	>4.8
Serratia marcescens	15 min.	3.2
	30 min.	>4.7
	45 min.	>4.7
	60 min.	>4.7
Candida albicans	15 min.	1.9
	30 min.	2.5
	45 min.	2.7
	60 min.	2.8
	4 hr.	3.4
Fusarium solani	15 min.	3.4
	30 min.	4.3
	45 min.	4.4
	60 min.	4.2
	4 hr.	>4.4

Based on the same criteria as described in Example 5, the alexidine solution formulated at 4.0 ppm is able to pass a stand-alone test (with no rub or rinse) at the 30 minute time point, 45 time point and the 60 minute time point. With respect to *Staphylococcus aureus* the 15 minute time point failed.

EXAMPLE 7

This Example shows the antimicrobial efficacy of a solution according to the present invention using the testing procedures described in Example 5 above. These tests were similar to Example 6 except with a different lot that had been aged for 18 months. The concentration of alexidine was formulated at 4.0 ppm and the time intervals were 15 minutes, 30 minutes, 45 minutes, and 60 minutes. The results are shown in Table 4 below.

TABLE 4

Microorganism	Soak Period	Log Reduction
Staphylococcus aureus	15 min.	3.7
	30 min.	4.7
	45 min.	>4.8
	60 min.	>4.8
Pseudomonas aeruginosa	15 min.	4.2
	30 min.	>4.8
	45 min.	>4.8
	60 min.	>4.8
Serratia marcescens	15 min.	3.0
	30 min.	4.7
	45 min.	>4.8
	60 min.	>4.8
Candida albicans	15 min.	1.0
	30 min.	1.7
	45 min.	1.9
	60 min.	2.1
	4 hr.	3.1
Fusarium solani	15 min.	2.4
	30 min.	>4.5
	45 min.	>4.5
	60 min.	>4.5
	4 hr.	>4.5

In the above testing, the alexidine passed the stand alone test at 30 minutes, 45 minutes, and 60 minutes, but only just passed the 15 minute stand-alone test with respect to *Serratia marcescens* and *Candida albicans*. It is clear that at 30 minutes, 45 minutes, and one hour stand-alone showed greater disinfection, easily passing the acceptance criteria.

EXAMPLE 8

This Example shows the antimicrobial efficacy of a solution according to the present invention using the testing procedures described in Example 5 above. For a final time, these tests were similar to Example 6 except with a different batch. The concentration of alexidine was formulated at 4.0 ppm and the time intervals were 15 minutes, 30 minutes, 45 minutes, and 60 minutes, which would represent 25%, 50% and 100% of a one hour minimum recommended disinfection period. The solution had been aged 19 months at 25°C. The results are shown in Table 5 below.

TABLE 5

Microorganism	Soak Period	Log Reduction
Staphylococcus aureus	15 min.	3.5
	30 min.	>4.9
	45 min.	>4.9
	60 min.	>4.9
Pseudomonas aeruginosa	15 min.	3.3
	30 min.	>4.8
	45 min.	>4.8
	60 min.	>4.8
Serratia marcescens	15 min.	2.5
	30 min.	4.6
	45 min.	>4.7
	60 min.	>4.7
Candida albicans	15 min.	0.9
	30 min.	1.7
	45 min.	1.8
	60 min.	1.9
	4 hr.	2.6
Fusarium solani	15 min.	3.6
	30 min.	>4.6
	45 min.	>4.6
	60 min.	>4.6
	4 hr.	>4.6

In the above test, the alexidine solution passed the stand-alone test (without rubbing) at 30 minutes, 45 minutes, and 60 minutes, but did not pass the test at 15 minutes, since at 15 minutes the log reduction for *Serratia marcescens* was less than 3 logs and the number of the yeast *Candida albicans* was not reduced by at least 1 log. The results in Tables 3, 4, and 5 above show some variation due to the testing of different lots of the solutions described in Example 4 above, but that a 4.0 ppm alexidine solution would require at least about 30 minutes in order to pass a stand-alone procedure without rubbing.

COMPARATIVE EXAMPLE 9

This Example compares the antimicrobial efficacy of a solution according to the present invention (such as formulated in Example 4) compared to an analogous solution containing only PHMB as the germicide. Both solutions were borate buffered to enhance the efficacy of the biguanide. The testing procedures used for evaluating the antimicrobial efficacy of disinfecting solutions was the same as in Example 5 above. The results are shown in Table 6 below.

TABLE 6

Microorganism Tested	Time Tested	1.0 ppm PHMB	4.0 ppm Alexidine•2HCl
Staphylococcus aureus	1 hr	3.5	>4.9
	2 hr	3.9	>4.9
	3 hr	>4.9	>4.9
	4 hr	>4.9	>4.9
Pseudomonas aeruginosa	1 hr	3.5	>4.8
	2 hr	4.0	>4.8
	3 hr	4.1	>4.8
	4 hr	>4.8	>4.8
Serratia marcescens	1 hr	3.2	3.7
	2 hr	4.2	>4.7
	3 hr	>4.7	>4.7
	4 hr	>4.7	>4.7
Candida albicans	1 hr	2.9	2.9
	2 hr	3.0	4.3
	3 hr	3.4	>4.7
	4 hr	3.4	3.9
	24 hr	4.3	4.6
Fusarium solani	1 hr	0.4	3.1
	2 hr	0.5	4.1
	3 hr	0.4	4.5
	4 hr	0.4	4.6
	24 hr	1.3	>4.6

As indicated in Example 5, the acceptance criteria was that the number of bacteria recovered per mL must be reduced by a factor of not less than 99.9% (3 logs) with the minimum disinfection period (which would be recommended with the product, in label, package, and/or package insert instructions), and the number of mold and yeast recovered per mL shall be reduced by a factor of not less than 90% (1 log) within the minimum recommended disinfection time, with no increase at four times the minimum recommended disinfection time. The above results show that the 1.0 ppm PHMB did not pass the one hour stand-alone test, since the *Fusarium solani*, a mold, was not sufficiently reduced. In contrast, the 4.0 ppm alexidine solution according to the present invention passed the one hour stand-alone test, showing a reduction in the number of mold by 3.1 log after 1 hour. Presently, PHMB is used in an amount of about 1.0 ppm in commercial

solutions for disinfecting soft lenses. It has been found that increasing the level of PHMB to 3.0 ppm results in clinical findings that suggest PHMB may be less safe than desirable, for use with soft contact lens. In contrast, as shown in the next example, based on rabbit studies, it has been found that a 4.0 ppm solution of alexidine would be very safe for human use in disinfecting soft lenses.

EXAMPLE 10

This example demonstrates the ocular toxicology of alexidine in solutions such as described in Example 4 above, but at various concentrations of the bis(biguanide). A series of formulations were prepared in which the amount of alexidine were, respectively 4 ppm (test 1), 6 ppm (test 2), 8 ppm (test 3), 10 ppm (test 4), 12 ppm (test 5), 15 ppm (test 6), 18 ppm (test 7) , 22 ppm (test 8), 27 ppm (test 9), 33 ppm (test 10), 40 ppm (test 11) and 50 ppm (test 12). These test solutions of alexidine were used in soaking J&J SureVue® (etafilcon A) lenses (soft lenses) in 2.5 mL of solution for 1 week or more in order to reach maximal alexidine uptake.

An ocular irritation screening study was conducted in the rabbit to determine the threshold for ocular irritation. Eyes treated with lenses were compared to a contralateral control eye. Treated lenses were placed on the right eye of rabbits; control lenses were placed on the left eye. Any lenses displaced from the eyes during the lens wear day were reinserted after rinsing with 0.9% sodium chloride USP solution (SC). Eyes were examined with the aid of a direct light source before lens placement, at 50-70 minutes, 7-8 hours, 23-24 hours, and 30-32 hours after placement. Macroscopic observations were recorded in accordance with criteria in the Draize* score system. The maximum total score is the sum of all scores obtained for the cornea, iris, and conjunctivae. Total maximum score possible is 110 per eye, 80 with respect to the cornea, 10 with respect to the iris, and 20 with respect to the conjunctivae.

The results of macroscopic ocular examinations for each animal appear in Table 7 below (weighted totals present).

---

* Draize, J.H., G. Woodward and H.O. Calvery. 1944. Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. J. Pharmacol. Exp. Ther. 82:377-390.

TABLE 7

Test No.	ppm Alexidine 2HCl	Prior to Lens Application		POST LENS APPLICATION							
				50-70 Minutes		7-8 Hours		23-24 Hours		30-32 Hours	
		R	L	R	L	R	L	R	L	R	L
1	4	0	0	2	2	2	0	2	0	2	2
2	4	0	0	2	2	2	2	2	2	2	2
3	4	0	0	2	2	2	2	2	2	2	2
4	6	2	0	2	2	2	0	2	0	2	0
5	6	2	2	2	2	2	2	2	2	2	2
6	6	2	2	2	2	2	0	2	0	2	0
7	8	0	0	2	0	2	0	2	2	2	2
8	8	2	2	2	2	2	2	2	0	2	2
9	8	2	2	2	2	2	2	2	2	2	2
10	10	2	0	2	0	4	0	2	0	2	0
11	10	2	2	2	0	2	0	2	2	2	2
12	10	0	0	2	0	4	2	0	0	0	0
13	12	2	0	2	2	2	2	2	2	2	2
14	12	2	2	2	2	2	2	2	2	2	2
15	12	2	2	2	2	2	2	2	2	2	2
16	15	0	0	2	2	4	0	2	0	2	0
17	15	2	2	4	2	4	0	2	2	2	2
18	15	0	0	2	0	4	0	0	0	2	0
19	18	2	0	2	2	6	2	2	0	2	0
20	18	2	2	2	2	6	2	2	2	2	2
21	18	2	2	2	2	6	2	2	2	2	2
22	22	2	0	2	2	11	0	2	0	2	2
23	22	2	2	2	2	11	0	2	0	2	2
24	22	0	0	2	0	11	0	2	0	2	0
25	27	2	0	2	2	13	2	2	2	2	0
26	27	2	0	2	2	11	2	2	2	2	0
27	27	2	2	2	2	6	2	2	2	2	0
28	27	2	0	2	2	11	2	7	2	7	2
29	27	2	0	2	2	11	2	7	2	7	2
30	27	2	0	2	2	9	0	2	0	2	0

R = Right (Test) Eye
L = Left (Control) Eye

When worn by rabbits, lenses soaked in 10 ppm Alexidine showed the first signs of increased ocular toxicity, with conjunctival reactions observed after 7-8 hours of lens wear. This sporadic conjunctival reaction was clearly defined at a dose of 15 ppm alexidine in solution and continued to become more severe as the dosage was elevated. Iridial involvement was observed at 22 ppm and corneal opacity was observed at 27 ppm. Conjunctival redness, chemosis, and discharge were the sole basis of the Draize findings for lens numbers until 22 ppm and 27 ppm (test nos. 8 and 9). Iritis, in addition to previously described findings were observed for lens number 8 and 9. The above results indicate that a formulation with 10 ppm of alexidine or more is not recommended for disinfecting soft contact lenses. The preferred formulation with 4 ppm alexidine, represents a 2.5-fold safety margin relative to the initial onset of any possible abnormal ocular health in rabbits.

EXAMPLE 11

This example illustrates the preparation of aqueous disinfecting solutions according to the present invention comprising a combination of alexidine and polyhexamtheylene biguanide (also referred to as PAPB or PHMB). The following components are used, in the indicated percent weight per total volume of the solution:

	Percent (w/v)
PHMB HCl	0.00008
Alexidine•2HCl	0.0002
Poloxamine 1107**	1.0
Na_2EDTA	0.11
Boric Acid	0.66
Sodium Borate	0.10
Sodium Chloride	0.54
Distilled Water (qs)	100.0

** molecular weight 14,500, 70% (w/v) Tetronic® 1107, a poly(oxypropylene) poly(oxyethylene) block copolymer adduct of ethylene diamine, a trademark of BASF Wyandotte Corp., Wyandotte, MI.

The solution is prepared by gradually heating 80 percent of the water to 80°C while dissolving the disodium EDTA therein. The boric acid and sodium borate are added to the heated solution of disodium EDTA and dissolved. The sodium chloride is then added to the solution and dissolved, followed by the addition of surfactants. The solution is sterilized by autoclaving to 120°C for 45 minute. After the solution is cooled to room temperature, the bis(biguanide) and the PAPB are added through a sterile filter, followed by the balance of distilled water. The solution is packaged in sterilized plastic containers.

EXAMPLE 12

This Example illustrates the improved antimicrobial efficacy of a combination of alexidine with polyhexamtheylene biguanide (PAPB) in an aqueous disinfecting solution for contact lenses. The testing procedures described in Example 5 above were followed to determine whether the primary performance criteria would be passed at time intervals of 5 minutes, 15 minutes, 30 minutes, and 4 hours. The concentration of alexidine in this set of tests was formulated in amounts ranging from 0.0 to 4.0 ppm in combination with either 0.0 (control) or 0.8 ppm alexidine, the latter the amount of PAPB currently used in commercial multi-purpose solutions for soft contact lenses. The results are shown in Table 8 below.

TABLE 8

Alexidine• 2HCl (ppm)	PAPB HCl (ppm)	Soak Period	Log Reduction *S. marcescens*	Log Reduction *C. albicans*
0.5	0.8	5 min.	-	0.6
		15 min.	2.0	1.1
		30 min.	3.2	1.8
		60 min.	4.3	3.5
1.0	0.8	5 min.	-	0.5
		15 min.	2.6	1.1
		30 min.	3.7	2.2
		60 min.	>4.3	4.2
2.6	0.8	5 min.	-	0.7
		15 min.	2.7	2.2
		30 min.	>4.3	3.3
		60 min.	>4.3	>4.2
4.0	0.8	5 min.	-	1.1
		15 min.	>4.3	3.0
		30 min.	>4.3	>4.2
		60 min.	>4.3	>4.2
0.5	0.0	5 min.	-	0.3
		15 min.	0.6	1.0
		30 min.	1.6	-0.2
		60 min.	2.5	-0.1
2.6	0.0	5 min.	-	0.4
		15 min.	2.2	0.5
		30 min.	>4.3	0.5
		60 min.	>4.3	1.4
0.0	0.8	15 min.	-	0.6
		30 min.	1.3	0.8
		45 min.	2.0	1.4
		60 min.	3.1	2.9

The results show that the addition of alexidine to the polyhexametheylene biguanide very significantly improved antimicrobial efficacy, with the improved efficacy reaching a trade-off, for practical purposes, at about 4.0 ppm, such that any improved antimicrobial efficacy would be unlikely to be justified by the increased potential for toxicity at higher concentrations of the antimicrobial agents. With respect to *C. albicans*, there appears to be a synergistic effect at time periods of 15 minutes and 30 minutes, with

the combination of 2.6 ppm alexidine and 0.8 ppm PAPB showing greater efficacy than the sum of 2.6 ppm alexidine by itself and 0.8 ppm PAPB by itself.

EXAMPLE 13

This example illustrates the preparation of an aqueous disinfecting solution according to the present invention comprising a combination of alexidine and polyhexamtheylene biguanide (also referred to as PHMB). The following components are used, in the indicated percent weight per total volume of the solution:

TABLE 9

	Percent (w/v)
PHMB	0.00008
Alexidine•2HCl	0.0002
Poloxamine 1107**	1.0
Na_2EDTA	0.11
Boric Acid	0.66
Sodium Borate	0.10
Sodium Chloride	0.54
Distilled Water (qs)	100.0

** molecular weight 14,500, 70% (w/v) Tetronic® 1107, a poly(oxypropylene) poly(oxyethylene) block copolymer adduct of ethylene diamine, a trademark of BASF Wyandotte Corp., Wyandotte, MI.

The solution is prepared by gradually heating 80 percent of the water to 80°C while dissolving the disodium EDTA therein. The boric acid and sodium borate are added to the heated solution of disodium EDTA and dissolved. The sodium chloride is then added to the solution and dissolved, followed by the addition of the surfactant. The solution is sterilized by autoclaving to 120°C for 45 minute. After the solution is cooled to room temperature, the alexidine bis(biguanide) and the PHMB are added through a sterile filter, followed by the balance of distilled water. The solution is packaged in sterilized plastic containers.

EXAMPLE 14

This Example illustrates the microbiocidal efficacy of solutions according to the present invention. The above testing procedures were used for evaluating the antimicrobial efficacy against C. *albicans* of disinfecting solutions such as prepared in Example 13, but which contain the bis(biguanide) alexidine at various concentrations extending from 1 ppm to 4 ppm and the biguanide polymer at various concentrations extending from 0.3 to 1.5 ppm. The results are shown in Table 10 after a 5 minute soak, Table 11 after a 15 minute soak, Table 12 after a 30 minute soak, and Table 13 after a 45 minute soak. Tables 14 to 17, corresponding respectively to Tables 10 to 13, compares the theoretical kill, based on the sum of individual disinfecting agents versus actual kill using the combination of disinfecting agents.

TABLE 10
(8 Minutes)

		PHMB			
		0 ppm	**0.3 ppm**	**0.8 ppm**	**1.5 ppm**
Alexidine	0 ppm	0.4	0.4	0.7	1.0
	1 ppm	0.5	0.6	0.9	1.1
	2 ppm	0.7	0.8	0.9	1.5
	3 ppm	0.8	1.1	1.6	2.6
	4 ppm	1.1	1.8	2.8	3.4

TABLE 11
(15 Minutes)

		PHMB			
		0 ppm	**0.3 ppm**	**0.8 ppm**	**1.5 ppm**
Alexidine	0 ppm	0.4	0.7	1.5	1.9
	1 ppm	0.4	1.1	2.2	2.9
	2 ppm	0.8	1.7	2.8	3.5
	3 ppm	1.6	2.7	3.7	4.5
	4 ppm	2.6	3.8	4.8	>4.8

TABLE 12
(30 Minutes)

		PHMB			
		0 ppm	**0.3 ppm**	**0.8 ppm**	**1.5 ppm**
Alexidine	0 ppm	0.4	1.0	2.1	3.1
	1 ppm	0.5	1.8	3.3	4.4
	2 ppm	1.2	2.1	3.7	4.5
	3 ppm	1.9	3.5	4.8	>4.8
	4 ppm	3.4	>4.8	>4.8	>4.8

TABLE 13
(45 Minutes)

		PHMB			
		0 ppm	**0.3 ppm**	**0.8 ppm**	**1.5 ppm**
Alexidine	0 ppm	0.4	1.1	3.0	4.1
	1 ppm	0.4	2.1	3.7	>4.8
	2 ppm	0.9	2.6	4.5	>4.8
	3 ppm	2.1	4.5	>4.8	>4.8
	4 ppm	3.7	4.8	>4.8	>4.8

TABLE 14
(5 Minutes)

	Log Kill	
Formulation	**Theoretical**	**Actual**
1 ppm Alex/0.3 ppm PHMB	0.9	0.6
2 ppm Alex/0.3 ppm PHMB	1.1	0.8
3 ppm Alex/0.3 ppm PHMB	1.2	1.1
4 ppm Alex/0.3 ppm PHMB	1.5	1.8
1 ppm Alex/0.8 ppm PHMB	1.2	0.9
2 ppm Alex/0.8 ppm PHMB	1.4	0.9
3 ppm Alex/0.8 ppm PHMB	1.5	1.6
4 ppm Alex/0.8 ppm PHMB	1.8	2.8
1 ppm Alex/1.5 ppm PHMB	1.5	1.1
2 ppm Alex/1.5 ppm PHMB	1.7	1.5
3 ppm Alex/1.5 ppm PHMB	1.8	2.6
4 ppm Alex/1.5 ppm PHMB	2.1	3.4

TABLE 15
(15 Minutes)

	Log Kill	
Formulation	**Theoretical**	**Actual**
1 ppm Alex/0.3 ppm PHMB	1.1	1.1
2 ppm Alex/0.3 ppm PHMB	1.5	1.7
3 ppm Alex/0.3 ppm PHMB	2.3	2.7
4 ppm Alex/0.3 ppm PHMB	3.3	3.8
1 ppm Alex/0.8 ppm PHMB	1.9	2.2
2 ppm Alex/0.8 ppm PHMB	2.3	2.8
3 ppm Alex/0.8 ppm PHMB	3.1	3.7
4 ppm Alex/0.8 ppm PHMB	4.1	4.8
1 ppm Alex/1.5 ppm PHMB	2.3	2.9
2 ppm Alex/1.5 ppm PHMB	2.7	3.5
3 ppm Alex/1.5 ppm PHMB	3.5	4.5
4 ppm Alex/1.5 ppm PHMB	4.5	4.8

TABLE 16
(30 Minutes)

	Log Kill	
Formulation	**Theoretical**	**Actual**
1 ppm Alex/0.3 ppm PHMB	1.5	1.8
2 ppm Alex/0.3 ppm PHMB	2.2	2.1
3 ppm Alex/0.3 ppm PHMB	2.9	3.5
4 ppm Alex/0.3 ppm PHMB	4.4	4.8
1 ppm Alex/0.8 ppm PHMB	2.6	3.3
2 ppm Alex/0.8 ppm PHMB	3.3	3.7
3 ppm Alex/0.8 ppm PHMB	4.0	4.8
4 ppm Alex/0.8 ppm PHMB	4.8	4.8
1 ppm Alex/1.5 ppm PHMB	3.6	4.4
2 ppm Alex/1.5 ppm PHMB	4.3	4.5
3 ppm Alex/1.5 ppm PHMB	4.8	4.8
4 ppm Alex/1.5 ppm PHMB	4.8	4.8

TABLE 17
(45 Minutes)

	Log Kill	
Formulation	**Theoretical**	**Actual**
1 ppm Alex/0.3 ppm PHMB	1.5	2.1
2 ppm Alex/0.3 ppm PHMB	2.0	2.6
3 ppm Alex/0.3 ppm PHMB	3.2	4.5
4 ppm Alex/0.3 ppm PHMB	4.8	4.8
1 ppm Alex/0.8 ppm PHMB	3.4	3.7
2 ppm Alex/0.8 ppm PHMB	3.9	4.5
3 ppm Alex/0.8 ppm PHMB	4.8	4.8
4 ppm Alex/0.8 ppm PHMB	4.8	4.8
1 ppm Alex/1.5 ppm PHMB	4.5	4.8
2 ppm Alex/1.5 ppm PHMB	4.8	4.8
3 ppm Alex/1.5 ppm PHMB	4.8	4.8
4 ppm Alex/1.5 ppm PHMB	4.8	4.8

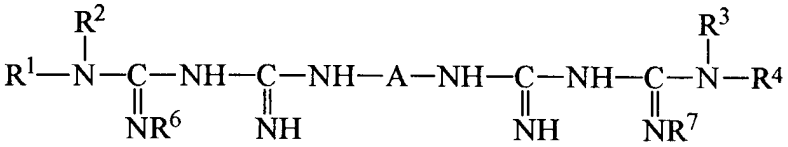
The above results show synergistic microbicidal effects against C. *albicans*, in which the log kill from the combination of both alexidine and PHMB, in a good proportion of cases, is higher than the sum of the individual disinfecting agents, which synergistic effects are evident, beginning with the results after 15 minutes. At 45 minutes, these synergistic effects may become less evident, when a higher proportion of the microorganisms have already been killed.

While the invention has been described in conjunction with specific examples thereof, this is illustrative only. Accordingly, many alternatives, modifications, and variations will be apparent to those skilled in the art in light of the foregoing description and it is, therefore, intended to embrace all such alternatives, modifications, and variations as to fall within the spirit and scope of the appended claims.

We claim:

1. A ophthalmically safe disinfecting solution for a contact lens comprising an aqueous solution comprising, in formulation, the following components:

(a) a microbiocidally effective amount of the hydrochloride salt of a bis(biguanide) in the amount of about 2.0 to about 8.0 ppm, or a corresponding molar amount of the bis(biguanide) in the form of another water-soluble salt or the free base, which bis(biguanide) has the following general formula:



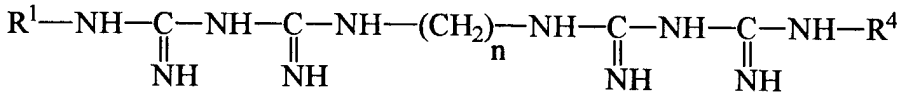
wherein R^1 and R^4 are independently selected from the group consisting of branched or unbranched alkyl having 4-12 carbon atoms, alkoxyalkyl ether or alkylsulfide radical having 4-12 carbon atoms, or cycloalkyl or cycloalkyl-alkyl radical having 5-12 carbon atoms; R^2 and R^3 are independently selected from the group consisting of hydrogen, alkyl having 1-12 carbon atoms, alkoxyalkyl having 1-12 carbon atoms, or cycloalkyl or cycloalkyl-alkyl having 5-12 carbon atoms; R^6 and R^7 are independently selected from the group consisting of hydrogen and alkyl radical having 1-6 carbon atoms, and A in the above formula is a divalent group having 4-16 carbon atoms and is selected from the group consisting of an alkylene, alkyloxyalkyl, and alkylsufide radical, wherein the aforesaid alkyoxyalkyl or alkylsulfide radicals are either a polymethylene chain interrupted with one or more oxygen and/or sulfur atoms or a polymethylene chain substituted with an alkoxy (-OR^8) or alkylthio (-SR^9) group, wherein R^8 and R^9 are independently selected from the group consisting of alkyl having 1-12 carbon atoms, or a cycloalkyl or cycloalkyl-alkyl having 5-12 carbon, or wherein A is a divalent polymethylene group having 8 to 16 carbon atoms interrupted with a divalent radical of cyclohexane or diaza-cyclohexane;

(b) an effective amount of a buffering agent;

(c) an effective amount of a surfactant; and

(c) water in an amount of at least about 90% by weight.

2. A ophthalmically safe disinfecting solution of claim 1 wherein the bis(biguanide) has the following formula:



wherein R^1 and R^4 are independently selected from the group consisting of branched or unbranched alkyl having 6 to 10 carbon atoms, alkoxyalkyl ether or alkylsulfide thioether radical having 6 to 10 carbon atoms and n is 5 to 7.

3. The ophthalmically safe disinfecting solution of claim 2 wherein R^1 and R^4 are a branched or unbranched alkyl having 6-10 carbon atoms.

4. The ophthalmically safe disinfecting solution disinfecting solution of claim 1, wherein the surfactant is a neutral or non-ionic surfactant in the amount of 0.01 to 5.0 percent.

5. The ophthalmically safe disinfecting solution disinfecting solution of claim 1, wherein the surfactant is a neutral or non-ionic surfactant having a plurality of poly(oxyalkylene) chains, each of the poly(oxyalkylene) comprises (-OR) repeat units, wherein R is independently an alkylene having 2 to 6 carbon atoms.

6. The ophthalmically safe disinfecting solution disinfecting solution of claim 5, wherein the surfactant is a neutral or non-ionic surfactant which comprises a block copolymer of poly(ethyleneoxide) and poly(propylene oxide) segments.

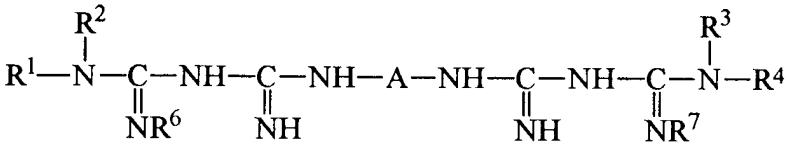
7. The disinfecting solution of claim 1, wherein the amount of the bis(biguanide) is 2.5 to 6.0 ppm.

8. The disinfecting solution of claim 1 wherein the amount of the bis(biguanide) is 3.0 to 5.0 ppm.

9. A method of disinfecting or cleaning and disinfecting a soft contact lens with a multipurpose solution or effective multipurpose solution, which method comprises:

(a) soaking the lens in a solution, such that acceptable disinfection of the contact lens is obtained within a minimum recommended soaking period, the solution comprising, in formulation, the following components:

(i) a microbiocidally effective amount of the hydrochloride salt of a bis(biguanide) in the amount of about 2.0 to about 8.0 ppm, or a corresponding molar amount of the bis(biguanide) in the form of another water-soluble salt or the free base, which bis(biguanide) has the following general formula:



wherein R^1 and R^4 are independently selected from the group consisting of branched or unbranched alkyl having 4-12 carbon atoms, alkoxyalkyl or alkylsulfide radical having 4-12 carbon atoms, or cycloalkyl or cycloalkyl-alkyl radical having 5-12 carbon atoms; R^2 and R^3 are independently selected from the group consisting of hydrogen, alkyl having 1-12 carbon atoms, alkoxyalkyl having 1-12 carbon atoms, or cycloalkyl or cycloalkyl-alkyl having 5-12, carbon atoms; R^6 and R^7 are independently selected from the group consisting of hydrogen and alkyl radical having 1-6 carbon atoms, and A in the above formula is a divalent group having 4-16 carbon atoms and is selected from the group consisting of an alkylene, alkyloxyalkyl, and alkylsufide radical, wherein the aforesaid alkyoxyalkyl or alkylsulfide radicals are either a polymethylene chain interrupted with one or more oxygen and/or sulfur atoms or a polymethylene chain substituted with an alkoxy (-OR^8) or alkylthio (-SR^9) group, wherein R^8 and R^9 are independently selected from the group consisting of alkyl having 1-12 carbon atoms, or a

cycloalkyl or cycloalkyl-alkyl having 5-12 carbon, or wherein A is a divalent polymethylene group having 8 to 16 carbon atoms interrupted with a divalent radical of cyclohexane or diaza-cyclohexane;

(ii) an effective amount of a buffering agent; and

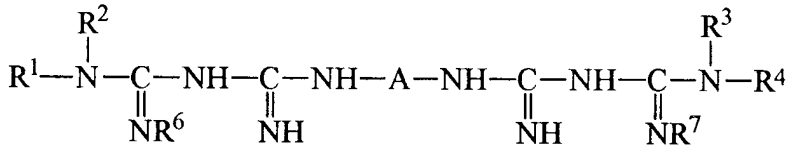
(iii) an effective amount of a surfactant; and

(b) directly placing the treated lens on the eye of the wearer, such that (ii) rinsing with a different solution prior to placement on the eye is not required, and (iii) no other solution is required for daily cleaning of the lens.

10. A method of disinfecting or cleaning and disinfecting a soft contact lens with a multipurpose solution or effective multipurpose solution, which method does not include rubbing, which method comprises:

(a) soaking the lens in a solution, such that acceptable disinfection of the contact lens is obtained without any rubbing of the lens with the solution, the solution comprising, in formulation, the following components:

(i) a microbiocidally effective amount of the hydrochloride salt of a bis(biguanide) in the amount of about 2.0 to about 8.0 ppm, or a corresponding molar amount of the bis(biguanide) in the form of another water-soluble salt or the free base, which bis(biguanide) has the following general:



wherein R^1 and R^4 are independently selected from the group consisting of branched or unbranched alkyl having 4-12 carbon atoms, alkoxyalkyl or alkylsulfide radical having 4-12 carbon atoms, or cycloalkyl or cycloalkyl-alkyl radical having 5-12, preferably 7-10 carbon atoms; R^2 and R^3 are independently selected from the group consisting of hydrogen, alkyl having 1-12 carbon atoms, alkoxyalkyl having 1-12 carbon atoms, or cycloalkyl or cycloalkyl-alkyl having 5-12, carbon atoms; R^6 and R^7 are independently selected from the group consisting of hydrogen and alkyl radical having 1-6 carbon atoms, and A in the above

formula is a divalent group having 4-16 carbon atoms and is selected from the group consisting of an alkylene, alkyloxyalkyl, and alkylsufide radical, wherein the aforesaid alkyoxyalkyl or alkylsulfide radicals are either a polymethylene chain interrupted with one or more oxygen and/or sulfur atoms or a polymethylene chain substituted with an alkoxy (-OR^8) or alkylthio (-SR^9) group, wherein R^8 and R^9 are independently selected from the group consisting of alkyl having 1-12 carbon atoms, or a cycloalkyl or cycloalkyl-alkyl having 5-12 carbon, or wherein A is a divalent polymethylene group having 8 to 16 carbon atoms interrupted with a divalent radical of cyclohexane or diaza-cyclohexane;

(ii) an effective amount of a buffering agent; and

(iii) an effective amount of a surfactant; and

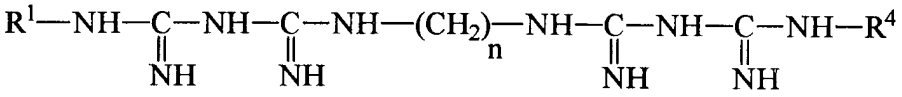
(b) directly placing the treated lens on the eye of the wearer, such that (i) rubbing of the lens with the same or a different solution is not required between the time the lens is removed from the eye and the time the lens following disinfection with the solution is replaced on the eye, (ii) rinsing with a different solution prior to insertion in the eye is not required, and (iii) no other solution is required for daily cleaning of the lens.

11. The method of claim 9 or 10, wherein the solution is used to clean a lens that is set or planned for replacement after not more than about 90 days of wear.

12. The method of claim 11, wherein the solution is used to clean a lens that is made from a polymer comprising about 0.0 to 5 mole percent repeat units derived from methacrylic acid (MAA), 10 to 99 mole percent of repeat units derived from hydroxyethyl methacrylate, and about 0.5 to 5 mole percent of cross-linking repeat units and wherein the lens is planned or set for replacement after not more than about 14 days of wear.

13. The method of claim 9 or 10, wherein the minimum required soaking period for lens care by the lens wearer is four hours or less.

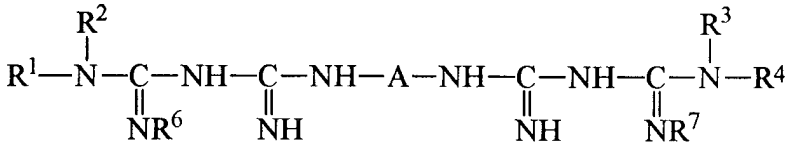
14. The method of claim 9, wherein the bis(biguanide) has the following formula:



or water-soluble salts thereof, wherein R^1 and R^4 are independently selected from the group consisting of branched or unbranched alkyl, alkoxyalkyl ether or alkylsulfide thioether radical, and n is 5 to 7.

15. A ophthalmically safe disinfecting solution for contact lenses comprising an aqueous solution comprising, before mixing, the following components:

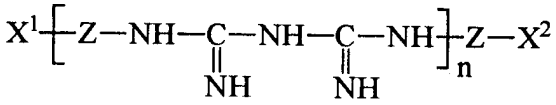
(a) a microbiocidally effective amount of the hydrochloride salt of a bis(biguanide) in the amount of about 0.10 to about 4.0 ppm, or a corresponding molar amount of the bis(biguanide) in the form of another water-soluble salt or the free base, which bis(biguanide) has the following general formula:



wherein R^1 and R^4 are independently selected from the group consisting of branched or unbranched alkyl having 4-12 carbon atoms, alkoxyalkyl ether or alkylsulfide radical having 4-12 carbon atoms, or cycloalkyl or cycloalkyl-alkyl radical having 5-12 carbon atoms; R^2 and R^3 are independently selected from the group consisting of hydrogen, alkyl having 1-12 carbon atoms, alkoxyalkyl having 1-12 carbon atoms, or cycloalkyl or cycloalkyl-alkyl having 5-12 carbon atoms; R^6 and R^7 are independently selected from the group consisting of hydrogen and alkyl radical having 1-6 carbon atoms, and A in the above formula is a divalent group having 4-16 carbon atoms and is selected from the group consisting of an alkylene, alkyloxyalkyl, and alkylsufide radical, wherein the aforesaid alkyoxyalkyl or alkylsulfide radicals are either a polymethylene chain interrupted with one or more oxygen and/or sulfur atoms or a polymethylene chain substituted with an alkoxy (-OR^8) or alkylthio (-SR^9) group, wherein R^8 and R^9 are independently selected

from the group consisting of alkyl having 1-12 carbon atoms or a cycloalkyl or cycloalkyl-alkyl having 5-12 carbons, or wherein A is a divalent polymethylene group having 8 to 16 carbon atoms interrupted with a divalent radical of cyclohexane or 1,4-diaza-cyclohexane;

(b) one or more polymeric biguanides, in the total amount of about 0.10 to about 3.0 ppm, having the formula:



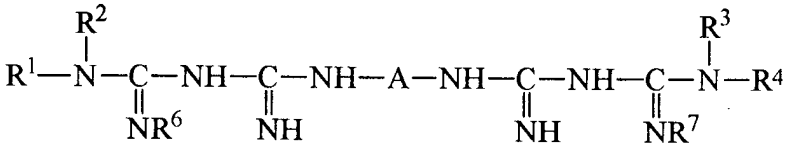
wherein Z is an organic divalent bridging group which may be the same or different throughout the polymer, n is on average at least 3, and X^1 and X^2 are independently selected from the groups $-NH_2$ and -NH - C(=NH) - NH - CN.

(c) an effective amount of a buffering agent;

(d) an effective amount of a surfactant; and

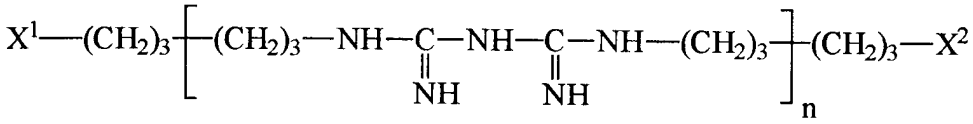
(e) water in an amount of at least about 90% by weight.

16. The ophthalmically safe disinfecting solution of claim 14 wherein the bis(biguanide) in (a) has the following formula:



wherein R^1 and R^4 are independently selected from the group consisting of branched or unbranched alkyl having 6 to 10 carbon atoms, alkoxyalkyl ether or alkylsulfide thioether radical having 6 to 10 carbon atoms and A is a divalent saturated chain having 4 to 12 carbon atoms.

17. The ophthalmically safe disinfecting solution of claim 14, comprising polymeric biguanides that are a mixture of molecules with the general formula:



wherein X^1 and X^2 are as defined above.

18. The ophthalmically safe disinfecting solution disinfecting solution of claim 14, wherein the surfactant is a neutral or non-ionic surfactant in the amount of 0.01 to 5.0 percent.

19. The ophthalmically safe disinfecting solution of claim 14, wherein the surfactant is a neutral or non-ionic surfactant having a plurality of poly(oxyalkylene) chains, each of the poly(oxyalkylene) comprises (-OR) repeat units, wherein R is independently an alkylene having 2 to 6 carbon atoms.

20. The ophthalmically safe disinfecting solution of claim 14, wherein the surfactant is a neutral or non-ionic surfactant which comprises a block copolymer of poly(ethyleneoxide) and poly(propylene oxide) segments.

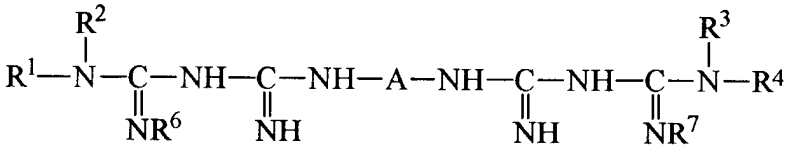
21. The ophthalmically safe disinfecting solution of claim 14, wherein the amount of the bis(biguanide) is 1.0 to 3.0 ppm.

22. The ophthalmically safe disinfecting solution of claim 14, wherein the amount of the polymeric biguanide is 0.1 to 2.0 ppm.

23. A method of disinfecting or cleaning and disinfecting a soft contact lens with a multipurpose solution or effective multipurpose solution, which method comprises:

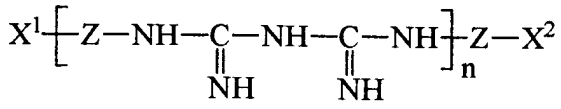
(a) soaking the lens in a solution, such that acceptable disinfection of the contact lens is obtained with the solution, the solution comprising, in formulation, the following components:

(i) a microbiocidally effective amount of the hydrochloride salt of a bis(biguanide) in the amount of about 0.1 to about 4.0 ppm, or a corresponding molar amount of the bis(biguanide) in the form of another water-soluble salt or the free base, which bis(biguanide) has the following general formula:



wherein R^1 and R^4 are independently selected from the group consisting of branched or unbranched alkyl having 4-12 carbon atoms, alkoxyalkyl ether or alkylsulfide radical having 4-12 carbon atoms, or cycloalkyl or cycloalkyl-alkyl radical having 5-12 carbon atoms; R^2 and R^3 are independently selected from the group consisting of hydrogen, alkyl having 1-12 carbon atoms, alkoxyalkyl having 1-12 carbon atoms, or cycloalkyl or cycloalkyl-alkyl having 5-12 carbon atoms; R^6 and R^7 are independently selected from the group consisting of hydrogen and alkyl radical having 1-6 carbon atoms, and A in the above formula is a divalent group having 4-16 carbon atoms and is selected from the group consisting of an alkylene, alkyloxyalkyl, and alkylsufide radical, wherein the aforesaid alkyoxyalkyl or alkylsulfide radicals are either a polymethylene chain interrupted with one or more oxygen and/or sulfur atoms or a polymethylene chain substituted with an alkoxy (-OR^8) or alkylthio (-SR^9) group, wherein R^8 and R^9 are independently selected from the group consisting of alkyl having 1-12 carbon atoms or a cycloalkyl or cycloalkyl-alkyl having 5-12 carbons, or wherein A is a divalent polymethylene group having 8 to 16 carbon atoms interrupted with a divalent radical of cyclohexane or 1,4-diaza-cyclohexane;

(ii) one or more polymeric biguanides in the amount of about 0.10 to about 3.0 ppm, which polymeric biguanides have the following general formula:



wherein Z is an organic divalent bridging group which may be the same or different throughout the polymer, n is at least 3, and X^1 and X^2 are independently selected from the groups $-NH_2$ and -NH - C - NH - CN.
NH

(iii) an effective amount of a buffering agent;

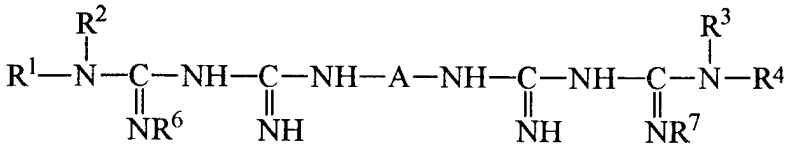
(iv) an effective amount of a surfactant present; and

(b) directly placing the treated lens on the eye of the wearer, wherein (i) rinsing with a different solution prior to replacement on the eye is not required, and (ii) no other solution is required for daily cleaning of the lens.

24. A method of disinfecting or cleaning and disinfecting a soft contact lens with a multipurpose solution or effective multipurpose solution, which method does not include rubbing, which method comprises:

(a) soaking the lens in a solution, such that acceptable disinfection of the contact lens is obtained without any rubbing of the lens with the solution, the solution comprising, before mixing, the following components:

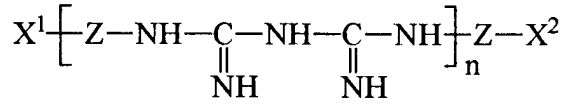
(i) a microbiocidally effective amount of the hydrochloride salt of a bis(biguanide) in the amount of about 0.10 to about 4.0 ppm, or a corresponding molar amount of the bis(biguanide) in the form of another water-soluble salt or the free base, which bis(biguanide) has the following general formula:

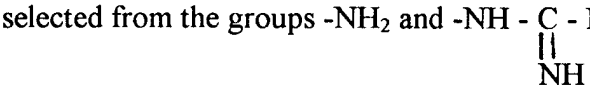


wherein R^1 and R^4 are independently selected from the group consisting of branched or unbranched alkyl having 4-12 carbon atoms, alkoxyalkyl ether or

alkylsulfide thioether radical having 4-12 carbon atoms, or cycloalkyl or cycloalkyl-alkyl radical having 5-12 carbon atoms; R^2 and R^3 are independently selected from the group consisting of hydrogen, alkyl having 1-12 carbon atoms, alkoxyalkyl having 1-12 carbon atoms, or cycloalkyl or cycloalkyl-alkyl having 5-12 carbon atoms; R^6 and R^7 are independently selected from the group consisting of hydrogen and alkyl radical having 1-6 carbon atoms, and A in the above formula is a divalent group having 4-16 carbon atoms and is selected from the group consisting of alkylene, alkyloxyalkyl, and alkylsufide radical, wherein the aforesaid alkyoxyalkyl or alkylsulfide radicals are either a polymethylene chain interrupted with one or more oxygen and/or sulfur atoms or a polymethylene chain substituted with an alkoxy ($-OR^8$) or alkylthio ($-SR^9$) group, wherein R^8 and R^9 are independently selected from the group consisting of alkyl having 1-12 carbon atoms or a cycloalkyl or cycloalkyl-alkyl having 5-12 carbons, or wherein A is a divalent polymethylene group having 8 to 16 carbon atoms interrupted with a divalent radical of cyclohexane or 1,4-diaza-cyclohexane;

(ii) one or more polymeric biguanides in the amount of about 0.10 to about 3.0 ppm, having the formula:



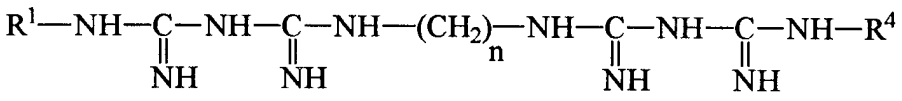
wherein Z is an organic divalent bridging group which may be the same or different throughout the polymer, n is on average at least 3, and X^1 and X^2 are independently selected from the groups $-NH_2$ and 

(iii) an effective amount of a buffering agent;

(iv) an effective amount of a surfactant present; and

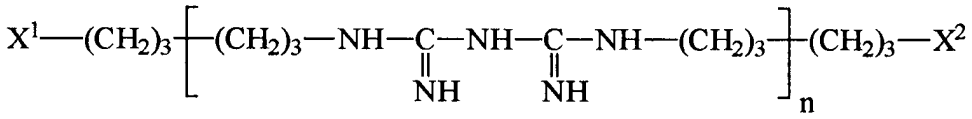
(b) directly placing the treated lens on the eye of the wearer, wherein (i) rubbing of the lens with the same or a different solution is not required between the time the lens is removed from the eye and the time the lens, following disinfection with the solution, is replaced on the eye, (ii) rinsing with a different solution prior to insertion in the eye is not required, and (iii) no other solution is required for daily cleaning of the lens.

25. The method of claim 22, wherein the bis(biguanide) has the following formula:



wherein R^1 and R^4 are independently selected from the group consisting of branched or unbranched alkyl, alkoxyalkyl ether and alkylsulfide thioether radical, and n is 5 to 7.

26. The method of claim 22, wherein the polymeric biguanides are a mixture of polymeric biguanides having the following formula:



wherein X^1 and X^2 are as defined above and n is on average 5 to 20.

27. The method of claim 22, wherein the solution is used to clean a lens that is set or planned for replacement after not more than about 30 days of wear.

28. The method of claim 27, wherein the lens is planned or set for replacement after not more than about 14 days of wear.

29. The method of claim 22, wherein the solution is used to clean a lens that is made from a polymer comprising about 0.0 to 5 mole percent repeat units derived from methacrylic acid (MAA), 10 to 99 mole percent of repeat units derived from hydroxyethyl methacrylate, and about 0.5 to 5 mole percent of cross-linking repeat units and

30. A kit for use by a contact-lens wearer for disinfecting or disinfecting and cleaning a contact lens, which kit comprising:

(a) a container with the ophthalmically safe disinfecting solution according to claim 1, and

(b) package instructions that comprise a directions for the contact lens wearer to carry out the method according to claim 10.

31. A kit for use by a contact-lens wearer for disinfecting or disinfecting and cleaning a contact lens, which kit comprises:

(a) a container with the ophthalmically safe disinfecting solution according to claim 14; and

(b) package instructions that comprise directions for the contact-lens wearer to carrying out the method according to claim 23.

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/US 97/20087

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A01N47/44 A61L2/16 A61L2/18

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)
IPC 6 A01N A61L

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 practical, 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.
X	US 5 096 607 A (MOWREY-MCKEE MARY F ET AL) 17 March 1992 See: col. 2, line 61 - col. 3, line 2; col. 5, line 41 to col. 6, line 37; tables I and II (examples 1-6;38-41).	1-14
A	EP 0 125 092 A (ICI PLC) 14 November 1984 cited in the application see page 9, line 1 - page 10, line 27	1-31
A	WO 94 15649 A (POLYMER TECHNOLOGY CORP) 21 July 1994 see the whole document	15-31
A	WO 90 11315 A (STOCKEL RICHARD F) 4 October 1990 see the whole document	15-31

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

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"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)

"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

"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

"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

"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.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
16 March 1998	03.04.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Klaver, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna..ial Application No
PCT/US 97/20087

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5096607 A	17-03-92	AT 113848 T	15-11-94
		AU 675414 B	06-02-97
		AU 3043992 A	11-02-93
		AU 628926 B	24-09-92
		AU 4998990 A	30-08-90
		CA 2009118 A,C	21-08-90
		DE 69013943 D	15-12-94
		DE 69013943 T	16-03-95
		EP 0384666 A	29-08-90
		ES 2066966 T	16-03-95
		HK 102695 A	30-06-95
		JP 2289255 A	29-11-90
		KR 9606144 B	09-05-96
EP 0125092 A	14-11-84	JP 59231062 A	25-12-84
		US 4670592 A	02-06-87
WO 9415649 A	21-07-94	AU 5992594 A	15-08-94
		BR 9405653 A	14-11-95
		CA 2152962 A	21-07-94
		CN 1116407 A	07-02-96
		EP 0690728 A	10-01-96
		JP 8507701 T	20-08-96
		MX 9400301 A	31-08-94
		US 5453435 A	26-09-95
WO 9011315 A	04-10-90	US 4891423 A	02-01-90
		EP 0668885 A	30-08-95