

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

CLEAR CARE* PLUS
Cleaning and Disinfecting Solution

3% Hydrogen Peroxide

Professed Standard

Contact Lens Disinfectant

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Date of Preparation:
December 11, 2015

Date of Revision:

Submission Control No: 177795
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Table of Contents

PART I: HEALTH PROFESSIONAL INFORMATION.....	3
SUMMARY PRODUCT INFORMATION	3
INDICATIONS AND CLINICAL USE.....	3
CONTRAINDICATIONS	3
WARNINGS AND PRECAUTIONS.....	4
ADVERSE REACTIONS.....	5
DRUG INTERACTIONS	6
DOSAGE AND ADMINISTRATION	6
OVERDOSAGE	7
ACTION AND CLINICAL PHARMACOLOGY	7
STORAGE AND STABILITY.....	9
SPECIAL HANDLING INSTRUCTIONS	9
DOSAGE FORMS, COMPOSITION AND PACKAGING	9
PART II: SCIENTIFIC INFORMATION	10
PHARMACEUTICAL INFORMATION.....	10
CLINICAL TRIALS.....	10
DETAILED PHARMACOLOGY	12
MICROBIOLOGY	16
TOXICOLOGY	16
REFERENCES	17
PART III: PATIENT MEDICATION INFORMATION	18

CLEAR CARE* PLUS
Cleaning and Disinfecting Solution

3% Hydrogen Peroxide

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Contact Lens Disinfectant	3% Hydrogen Peroxide	None <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

INDICATIONS AND CLINICAL USE

CLEAR CARE* PLUS Cleaning and Disinfecting Solution is indicated for use in simultaneous cleaning, daily protein removal, disinfection, and storing of soft (hydrophilic) contact lenses (including silicone hydrogel lenses) and rigid gas permeable (fluoro silicone acrylate and silicone acrylate) contact lenses, as recommended by your eye care professional.

Geriatrics (> 65 years of age):

In the clinical studies, no meaningful differences in the types of AEs observed in geriatric subjects relative to those reported in adult subjects (18 to 64 years of age) was observed.

Pediatrics (2 - 17 years of age):

In the clinical studies, no meaningful differences in the types of AEs observed in pediatric patients relative to those reported in the adult and geriatric populations was observed.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph
- NEVER use CLEAR CARE PLUS for heat disinfection

WARNINGS AND PRECAUTIONS

General

The patient should be advised:

Serious Warnings and Precautions

The red snap cap and dropper tip means that this product is NOT FOR DIRECT USE ON EYE.

NEVER put CLEAR CARE PLUS into your eye OR onto a contact lens immediately before inserting the lens into your eye. Lenses must be soaked in the provided lens case for at least 6 hours to neutralize the solution prior to insertion. OTHERWISE, BURNING AND STINGING WILL RESULT. If you accidentally insert a non-neutralized lens, remove it immediately and rinse the open eye with plenty of water or sterile saline for a few minutes. If burning or stinging continues, seek immediate assistance from an eye care professional before resuming contact lens wear.

NEVER clean or rinse your contact lenses in your hands with CLEAR CARE PLUS. A mild, temporary skin discoloration (bleaching) of the fingers or hands may result from contact with non-neutralized solution. Always wash, rinse and dry your hands after exposure.

- To maintain product efficacy:
 - Only use the provided lens case with CLEAR CARE PLUS for disinfection and neutralization. Do not use a flat case. Do not use another solution with the provided lens case.
 - NEVER re-use solution in your lens case.
 - NEVER dilute or mix CLEAR CARE PLUS with any solution. Generic hydrogen peroxide may contain ingredients that have not been tested for ocular safety and may discolor or damage your contact lenses.
- To avoid product contamination:
 - NEVER touch the open bottle tip to any surface.
 - NEVER transfer the solution to another container.
- NEVER allow your lenses to come into contact with non-sterile liquids, including tap water and saliva.
- NEVER clean your lenses with a separate cleaner immediately prior to using CLEAR CARE PLUS. Any residual cleaner on the lenses will result in foaming, potentially causing the solution to overflow from the lens case resulting in incomplete neutralization of the solution.
- Tell your eye care professional about the medications you take. Some medications may affect contact lens wear.

- NEVER ingest CLEAR CARE PLUS, or gastric distress will result. If non-neutralized solution is ingested, immediately drink large amounts of water and seek medical assistance.
- Keep out of reach of children.

Problems with contact lenses and lens care products could result in serious injury to your eye. Follow your eye care professional's directions and all labeling instructions for proper use and care of your lenses and lens care products, including the lens case.

CLEAR CARE PLUS users should be advised of the following precautions:

- Always wash, rinse and dry your hands before handling your lenses.
- Always use the new lens case provided with each purchase of CLEAR CARE PLUS.
- Do not use if the security seal around the bottle cap is broken or missing or if the bottle or lens case is damaged.
- Tightly close the snap cap on the bottle after each use.
- Discard any remaining solution 3 months after first opening.
- Never use the solution after expiry date.
- Always use the solution between 15°C and 30°C as neutralization below 15°C may take longer than 6 hours.
- Consult your eye care professional before changing lens care products.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The following problems may occur with any contact lens wear: eyes sting, burn or itch (irritation), comfort is less than when lens was first placed on the eye, feeling of something in the eye (foreign body, scratched area), excessive watering (tearing) of the eye, unusual eye secretions, redness of the eye, reduced sharpness of vision (poor visual acuity), blurred vision, rainbows or halos around objects, sensitivity to light (photophobia), or dry eyes (see Warnings and Precautions).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

The clinical development of CLEAR CARE PLUS consisted of 2 clinical studies (C-13-003 and C-13-004) of 90 days duration. During these studies, 309 subjects (618 eyes) used CLEAR CARE PLUS as their lens care regimen. Of the 309 subjects, 238 (476 eyes) were soft contact lens wearers (hydrogel or silicone hydrogel) and 71 (142 eyes) were rigid gas permeable wearers

(silicone acrylate or flurosilicone acrylate).

No serious ocular adverse events were reported with the use of CLEAR CARE PLUS. Adverse events assessed by the examining physician as related to the use of CLEAR CARE PLUS reported at an incidence of $\geq 1\%$ in clinical trials (data pooled) included the event of eye irritation (1.5%). All other adverse events related to the use CLEAR CARE PLUS were reported at an incidence of less than 1% (see list below).

Less Common Clinical Trial Adverse Events (<1%)

The list below summarizes adverse events reported related to the use of CLEAR CARE PLUS at an incidence of $< 1\%$ in clinical trials (data pooled) and are presented in alphabetical order within the System Organ Classification.

Eye disorders: abnormal sensation in eye, conjunctival hyperaemia, eye pain, lacrimation increased, ocular discomfort, ocular hyperaemia, and punctate keratitis.

DRUG INTERACTIONS

Overview

In vitro lens compatibility studies with CLEAR CARE PLUS have shown that the lens care product is compatible with soft contact lenses from ISO Groups I, II and IV hydrogels as well as Group V silicone hydrogels and rigid gas permeable (RGP) contact lenses. Drug interaction studies with CLEAR CARE PLUS and other ophthalmic solutions, *in vivo* or *in vitro*, have not been performed.

DOSAGE AND ADMINISTRATION

The patient should be advised:

Never put CLEAR CARE PLUS on your lenses and insert directly into your eye. Otherwise, burning and stinging will result. If spillage occurs, clean up immediately with a paper towel. Wash, rinse and dry your hands before handling your lenses or touching your eyes.

1. Wash, rinse your hands and dry them with a clean towel.
2. Open the lens holder marked “L”. Remove your left lens and place it on the dome. Close the lens holder taking care to avoid damaging your lens.
3. Repeat the procedure with your right lens by placing it on the dome of the lens holder marked “R”.
4. Open the snap cap on the bottle of the CLEAR CARE PLUS and bend it back and out of the way.
5. Taking care not to splash yourself, thoroughly rinse the lenses in the lens holders with CLEAR CARE PLUS for 5 seconds.
6. Fill the CLEAR CARE cup to the fill line with CLEAR CARE PLUS. DO NOT UNDERFILL OR OVERFILL.
7. Place lens holders into the cup of the lens case and screw the cap closed. DO NOT SHAKE THE LENS CASE. Do not over tighten the lens case (only tighten finger tight).

8. Store the CLEAR CARE lens case upright.
 - If bubbles leak from the hole in the top of the lens case cap, non-neutralized CLEAR CARE PLUS solution may be present. Empty the solution from the lens case and thoroughly rinse the lens cup and lens holder with sterile saline or fresh CLEAR CARE PLUS. Clean up any spillage with a paper towel. Thoroughly wash, rinse and dry your hands before handling your lenses or touching your eyes. REPEAT THE DISINFECTION PROCEDURE ABOVE.
9. Allow lenses to soak for at least 6 hours to neutralize solution.

You will see the bubbling action of 3% hydrogen peroxide working to kill microorganisms that can cause serious infections, and remove protein, dirt and build-up. After neutralization, no preservatives or harsh chemicals enter your eye. The disc neutralizes the active disinfectant to create a gentle saline solution close to your own tears.
10. After washing, rinsing and drying your hands, remove your lenses from lens holder.
11. Your lenses are now ready to wear.
12. Discard used solution, rinse the CLEAR CARE lens cup and lens holder with sterile saline or fresh CLEAR CARE PLUS - DO NOT USE TAP WATER OR NON-STERILE WATER.
13. Turn the lens holder upside down outside the cup and allow both to air dry.
14. If you do not intend to wear your lenses immediately after disinfection/neutralization, you may store them in the neutralized CLEAR CARE PLUS in the unopened CLEAR CARE lens case for up to 14 days. After this time, your lenses must be cleaned and disinfected with CLEAR CARE PLUS prior to wear.

If recommended by your eye care professional: Rinse lenses with sterile saline before insertion.

OVERDOSAGE

Not applicable.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

When used as directed, CLEAR CARE PLUS provides a unique cleaning action, which removes film and debris from the lens surface. CLEAR CARE PLUS also helps prevent serious eye infections by killing harmful microorganisms on contact lenses including activity against *Acanthamoeba*.

CLEAR CARE PLUS Cleaning and Disinfecting Solution is a modification of the currently marketed, CLEAR CARE Cleaning & Disinfecting Solution, to include a proprietary block copolymer as a contact lens wetting and lubricating agent (referred to as EO₁₀BO₅ or HydraGlyde* Moisture Matrix or HydraGlyde). Like CLEAR CARE, CLEAR CARE PLUS is a 3% hydrogen peroxide solution intended for cleaning, protein removal, disinfecting and storing of hydrogel and silicone hydrogel soft contact lenses and rigid gas permeable (RGP) contact lenses. The addition of EO₁₀BO₅ in CLEAR CARE PLUS provides desired benefits of contact lens wetting and lubrication while maintaining the key chemical attributes, disinfection and preservative effectiveness efficacy, lens compatibility, biocompatibility and clinical performance

as CLEAR CARE for use with hydrogel and silicone hydrogel soft contact lenses and RGP lenses.

EO₁₀BO₅ is composed of poly(oxyethylene) and poly(oxybutylene) repeating units, similar to PLURONIC 17R4†, a block copolymer with repeating units of poly(oxyethylene) and poly(oxypropylene). The concentration of EO₁₀BO₅ in the formulation (0.04%) was optimized to provide effective lens wetting and safety.

A key surface chemistry property of the EO₁₀BO₅ block copolymer is the ability to improve the wettability of soft contact lenses. The improved lens wettability results from EO₁₀BO₅ masking hydrophobic sites on the lenses. The mechanism by which this occurs, particularly for silicone hydrogels, is interaction of the BO copolymer segments with the hydrophobic domains of the lenses and allowing for the retention of water/moisture on the lens surface due to the exposure of the hydrophilic EO copolymer units on the lens surface. In addition, the EO₁₀BO₅ adsorbs/absorbs to various lens materials and provides improvement in friction for silicone hydrogel lenses. The advantages for lens wetting chemistry and moisture loving properties reflect the physicochemical properties of the EO₁₀BO₅ chemistry including: 1) highly efficient interaction at the lens surface, 2) efficient masking of hydrophobic surfaces, and 3) substantivity or retention to hydrophobic surfaces.

Except for the addition of EO₁₀BO₅, CLEAR CARE PLUS is identical to the currently marketed CLEAR CARE product. Specifically, like CLEAR CARE, the modified formulation uses the same peroxide-based solution (3% hydrogen peroxide) as the active ingredient to kill germs and bacteria; phosphate buffer system; PLURONIC† 17R4 detergent-surfactant for no-rub cleaning) and is part of a chemical disinfection lens care system that includes a specialized lens case consisting of a transparent cup with a connected unit of screw cap, lens holders (baskets) and platinum-coated neutralization disc.

Rate of Product Neutralization

The rate of neutralization of CLEAR CARE PLUS during use with the lens case was evaluated by measuring peroxide concentration of the product at various time points during the six-hour neutralization cycle. Rapid neutralization readily occurs within the first several minutes, and the level of residual peroxide continues to decrease to less than 100 ppm after two hours. By the end of the indicated neutralization cycle of six hours, residual peroxide in the solution is less than 10 ppm.

Residual Hydrogen Peroxide (H₂O₂) Post Neutralization pH and Tonicity (Osmolality)

The neutralization profile of CLEAR CARE PLUS was conducted with CLEAR CARE solution as a control using the CLEAR CARE lens case. Neutralization cycles were performed at room temperature for a minimum of six hours. For both CLEAR CARE PLUS and CLEAR CARE solutions, five CLEAR CARE lens cases per peroxide system were evaluated. The neutralization tests with both solutions were carried through 100 cycles without a contact lens.

The residual hydrogen peroxide (H₂O₂) of the neutralized solution was measured via UV spectroscopy in parts per million (ppm) after 1, 15, 30, 45, 60, 75, 90 and 100 usage cycles at 6 hour neutralization. At each test interval, pH and tonicity (osmolality) were also measured post 6

hour neutralization.

The mean residual peroxide for both CLEAR CARE PLUS and CLEAR CARE solutions was less than 20 ppm throughout the study. In fact, the mean residual peroxide for both solutions was below 5 ppm after 100 cycles. There was no significant difference in residual peroxide levels between the two peroxide systems at any of the eight test cycle intervals. The mean pH for both CLEAR CARE PLUS and CLEAR CARE solutions ranged from 6.8 to 6.9, which is near neutral pH. The mean osmolality for both CLEAR CARE PLUS and CLEAR CARE solutions ranged from 290-293 mOsm/kg at each test cycle up to 100 cycles.

STORAGE AND STABILITY

CLEAR CARE PLUS Cleaning and Disinfecting Solution should be stored below 30°C and out of direct sunlight. Once bottle is opened, discard any remaining solution after 3 months of first opening.

SPECIAL HANDLING INSTRUCTIONS

Do not use if security seal around the bottle cap is broken or missing.

DOSAGE FORMS, COMPOSITION AND PACKAGING

The CLEAR CARE PLUS Cleaning and Disinfecting Solution system consists of: the CLEAR CARE PLUS Cleaning and Disinfecting Solution and the special CLEAR CARE lens case (the lens case). The lens case consists of a transparent cup (the cup) and a connected unit of screw cap, lens holders (baskets) and the neutralizer catalyst disc attached at the bottom. CLEAR CARE PLUS and the special lens case must always be used together.

CLEAR CARE PLUS is a sterile, preservative-free, buffered aqueous solution containing 3% hydrogen peroxide (active), a wetting agent (HydraGlyde* Moisture Matrix [EOBO-21* – polyoxyethylene-polyoxybutylene], phosphonic acid (stabilizer), a cleaning agent poloxamer surfactant (PLURONIC[†] 17R4), purified water, sodium chloride (0.79%) as the tonicity agent, sodium phosphate (monobasic and dibasic salts for pH buffer). Sodium hydroxide or phosphoric acid is sometimes added to maintain proper pH balance. HydraGlyde* Moisture Matrix is a proprietary multi-functional block copolymer that is primarily designed for wetting and lubricating silicone hydrogel lenses.

CLEAR CARE PLUS is supplied sterile in 90 mL, 360 mL and 480 mL sizes. The bottles are marked with the lot number and expiration date. A new lens case is supplied with each purchase.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: hydrogen peroxide

Chemical name: hydrogen peroxide

Molecular formula and molecular mass: H₂O₂, molecular weight - 34.0138

Structural formula: HO - OH

Physicochemical properties: Clear, colourless liquid with ozone-like odour

CLINICAL TRIALS

Study demographics and trial design

Table 2 - Summary of patient demographics for clinical trials CLEAR CARE PLUS Cleaning and Disinfecting Solution

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range)	Gender
C-13-003	Multicenter, prospective, randomized, observer-masked, active control, parallel group, safety and efficacy study	Overnight soak in solution, on a daily basis, after contact lens removal	Total, N=352	34.8 (10-71)	M: 86 F: 266
			Clear Care Plus, n=239	34.5 (10-71)	M: 65 F: 174
			Renu [†] fresh multi-purpose solution, n=113	35.3 (11-64)	M: 21 F: 92

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n = number)	Mean age (Range)	Gender
C-13-004	Multicenter, prospective, randomized, observer-masked, active control, parallel group, safety and efficacy study	Overnight soak in solution, on a daily basis, after contact lens removal	Total, N=106 Clear Care Plus, n=71 Boston Simplus [†] Multi-Action Solution, n= 35	52.1 (18-71) 52.9 (30-70) 50.5 (18-71)	M: 23 F: 83 M: 16 F: 55 M: 7 F: 28

Two clinical studies (C-13-003 and C-13-004) were conducted using CLEAR CARE PLUS. The designs of these two studies were very similar. Both studies were multicenter, prospective, actively controlled, and randomized. Both studies had 90-day durations with planned evaluation visits at Days 7, 30, 60, and 90. Both studies employed the same assessments:

- Lens Cleanliness as evaluated by an investigator-graded scale
- Contact Lens Corrected Distance Visual Acuity
- Slit-Lamp Biomicroscopy
- Average Lens Wearing Time
- Unscheduled Lens Replacement Incidence and Causality
- Subjective Assessments of Comfort, Vision, and Lens Handling
- Adverse Event Reporting
- Device Deficiency Reporting

The differences between the two studies were in the lens wearing populations and the control lens care solutions. C-13-003 enrolled wearers of soft contact lenses. Lenses included three different traditional hydrogel lens materials, and four different silicone hydrogel lens materials (one representative from each of the major contact lens manufacturers). C-13-004 enrolled gas permeable contact lens wearers. Only two different lens materials were included in this study, silicone acrylate and fluoro silicone acrylate. In both studies, the randomization ensured a balance of test and control solutions within each lens brand.

Study C-13-003 used Renu Fresh Multi-purpose Solution as the control, while C-13-004 used Boston Simplus Multi-Action Solution. Each control solution was chosen because of their indications for use with the respective study's lens materials (i.e. Renu for soft lenses and Boston Simplus for GP lenses); and it was expected that these lens care solutions would have similar safety profiles as CLEAR CARE PLUS.

Upon review of the results from both clinical trials, it was determined that CLEAR CARE PLUS is safe and effective when used as indicated for both soft (traditional hydrogel and silicone hydrogel) and gas permeable contact lenses as all safety and efficacy endpoints were met. The overall incidence of adverse events was low, and those that were reported are known risks that are commonly associated with general contact lens use.

Additionally, in both studies subjects were asked to either agree or disagree with the following comfort statement: “When I use this solution, my lenses are comfortable all day”, 83.4% of CLEAR CARE PLUS users either agreed or strongly agreed to the statement in the C-13-003 study ($p < 0.0001^1$); and 81.2% of CLEAR CARE PLUS users had the same response in the C-13-004 study ($p < 0.0001^1$).

Finally, in both studies subjects were also asked to respond to a statement about their vision: “When I use this solution, at the end of the lens wearing day, my vision is clear”. In the C-13-003 study, 83.8% of CLEAR CARE PLUS users either agreed or strongly agreed study ($p < 0.0001^1$); while in the C-13-004 study, 78.3% of CLEAR CARE PLUS users either agreed or strongly agreed to the statement study ($p < 0.0001^1$).

DETAILED PHARMACOLOGY

Disinfection Efficacy

The disinfection efficacy of CLEAR CARE PLUS was evaluated in a standard series of studies, including Stand-alone and Regimen tests based on ISO, ANSI standards and FDA guidelines. The Stand-alone test method evaluates the antimicrobial activity of a product at specified time intervals with and without soil. In addition, samples of CLEAR CARE PLUS prepared with 90% of hydrogen peroxide label claim (representing the minimum concentration specification for these compounds) were evaluated for antimicrobial activity. Results indicate that the formulations met the primary criteria of the Stand-alone test.

The Regimen test method is used to establish instructions for cleaning, rinsing and disinfecting (soaking) contact lenses. Four representative silicone hydrogel, three representative traditional soft hydrogel and two representative RGP contact lenses were challenged with the five ISO microorganisms. CLEAR CARE PLUS was used to rinse (5 seconds total) and disinfect (soak for 6 hours in lens case) the lenses. Following the 6 hour disinfection time, the lenses and corresponding soaking solutions were evaluated for residual microorganisms. Results indicate CLEAR CARE PLUS meets the EN ISO 14729:2001 and ANSI Z80 test criteria for traditional soft hydrogel, silicone hydrogel and RGP contact lenses.

The preservative effectiveness testing was based upon the current ISO standard EN ISO 14730:2000. Microorganisms used in these studies included Gram-positive (*Staphylococcus aureus* ATCC 6538), Gram-negative (*Pseudomonas aeruginosa* ATCC 9027 and *Escherichia coli* ATCC 8739) bacteria, yeast (*Candida albicans* ATCC 10231) and mold (*Aspergillus brasiliensis* ATCC 16404).

¹ P-values represent a within-group (CLEAR CARE PLUS only) test of the proportion of subjects who agreed or strongly agreed compared to 0.50.

Six stability lots of CLEAR CARE PLUS were evaluated for preservative effectiveness through 28 days. Each lot was inoculated initially and again at day 14 (rechallenge) with each of 5 representative microorganisms. The inoculated samples were evaluated for viability at days 7, 14, 21 and 28. Results demonstrated that all 6 stability lots met the EN ISO 14730 rechallenge preservative effectiveness test (PET) criteria through 28 days. In addition, samples of CLEAR CARE PLUS prepared with 90% hydrogen peroxide (2.7% w/v) met the EN ISO 14730 PET criteria over a 28-day period.

The Discard Date test, simulating long-term use of the product after the container has been opened, was conducted based on the EN ISO 14730, Annex C. The results indicate that CLEAR CARE PLUS is adequately preserved to maintain the antimicrobial quality of the product throughout the three months simulated in-use period and supports a discard date after opening of three (3) months, according to EN ISO 14730:2000.

CLEAR CARE PLUS stored in the unopened lens case and in the presence of organic soil, was evaluated for disinfection/preservative effectiveness over a 14-day test period based on EN ISO 14730 and the FDA 510(k) guidance document. The assay evaluated the effectiveness of CLEAR CARE PLUS at reducing and/or inhibiting the propagation of microorganisms after 6 hours, 24 hours, 3 days, 7 days and 15 days. Results from the study demonstrate that CLEAR CARE PLUS is capable of reducing and/or inhibiting the propagation of microorganisms over a 14-day period in an unopened lens case.

Microbiological studies were conducted to evaluate the antimicrobial activity of CLEAR CARE PLUS against *Acanthamoeba spp.* (*A. castellanii* and *A. polyphaga*) cysts and trophozoites. Results indicate that CLEAR CARE PLUS demonstrates anti-amoebal activity against cysts and trophozoites of *Acanthamoeba spp.*

Lens Compatibility

Lens compatibility studies were conducted in accordance with EN ISO 11981:2009 and EN ISO 18369-2:2012 to determine the lens/product compatibility of CLEAR CARE PLUS with representative soft contact lenses from ISO Groups I, II and IV hydrogels as well as Group V silicone hydrogels and two brands of RGP lenses.

The compatibility of CLEAR CARE PLUS with the test lenses was determined by evaluating changes in physical and/or optical parameters after the completion of 30 cycles of a simulated use regimen. For soft contact lenses, the lens parameters measured were diameter, dioptric power, base curve, light transmittance and UV transmittance (for lenses containing UV blocker). For RGP lenses, the lens parameters measured were diameter, dioptric power, base curve.

The studies demonstrated that the use of CLEAR CARE PLUS does not affect the physical or optical parameters of traditional soft hydrogel, silicone hydrogel or RGP contact lenses. Based on these study results, CLEAR CARE PLUS is compatible with traditional hydrogel and silicone hydrogel soft contact lenses and RGP contact lenses.

Lens Cleaning

A study was conducted to evaluate the *in vitro* cleaning efficacy of CLEAR CARE PLUS, with

multiple lens brands [including lenses in Group I and Group IV hydrogels, Group V silicone hydrogels and non-hydrogel rigid gas permeable (RGP) lenses)] using the Cleaning Image Analysis System (CIAS).

The lenses were deposited using an exaggerated *in vitro* lysozyme deposition model and cleaned for six hours in the AOCup (i.e. CLEAR CARE lens cup) using the disinfection and cleaning regimen for CLEAR CARE PLUS. The regimen includes rinsing each lens for five seconds with CLEAR CARE PLUS and submerging into fresh CLEAR CARE PLUS. For all lenses tested, images were taken before deposit (BD), after deposit (AD) and after cleaning (AC). The mean % cleaned (for each lens and each lens brand as a whole) was analyzed and calculated (based upon the BD, AD and AC images) using the CIAS software.

The percent cleaning efficacy ranged from 28% to 76% for the lens brands tested. The results of this study show that all lens brands tested (which include Group I and Group IV hydrogels, Group V silicone hydrogels and RGP lenses), demonstrated some level of lysozyme cleaning efficacy with CLEAR CARE PLUS.

An *in vitro* test was conducted to assess the ability of CLEAR CARE PLUS to remove protein from three different contact lens materials. Briefly, lenses were doped overnight in an artificial tear fluid solution and then either extracted immediately or cycled through CLEAR CARE PLUS for six hours and extracted. Sample analysis was conducted via the bicinchoninic acid assay (BCA). Comparison of the two data sets within each lens material yielded percent cleaning values of 92.87%, 24.10%, and 61.85% for ACUVUE[†] ADVANCE[†], FREQUENCY[†] 55, and PUREVISION[†]2, respectively, demonstrating the ability of CLEAR CARE PLUS to clean protein from these three lens types when doped with a physiologically-relevant multi-component artificial tear fluid solution.

Critical Micelle Concentration

The Critical Micelle Concentration (CMC) of CLEAR CARE PLUS was measured to support the cleaning effectiveness claim according to Appendix B of the May 1997 FDA contact lens care guidance. The CMC is the value obtained by extrapolating the data above the range of formulations' concentrations where virtually no micelles form, and the area below the range where virtually all additional surfactant concentrations form micelles. The value obtained where these ranges intersect is the CMC.

This study demonstrates that the CMC of CLEAR CARE PLUS is approximately 0.0035% w/v. The concentrations of Pluronic[†] 17R4 and the block copolymer ethyleneoxide butyleneoxide (EO₁₀BO₅) in CLEAR CARE PLUS are targeted at 0.05% w/v and 0.04% w/v respectively, for a total surfactant concentration of 0.09% w/v.

The total surfactant concentration of 0.09% w/v exceeds the CLEAR CARE PLUS formulation's CMC by approximately 26 times. Therefore, the concentration of the surfactants in CLEAR CARE PLUS is sufficient to ensure the cleaning performance of the product.

Lens Wettability

Reconditioning/rewetting with CLEAR CARE PLUS was evaluated on silicone hydrogel (SiHy)

lenses, as well as on other contact lens material groups. Lenses were evaluated for wetting via contact angle measurements immediately out-of-pack (OOP). The same lenses were equilibrated overnight in phosphate buffered saline and contact angle measurements obtained. Finally, the same lenses were treated in 10 mL of CLEAR CARE PLUS and contact angle measurements obtained. Prior to obtaining measurements for each step, lenses were exposed to air for 45 seconds each on both contact lens surfaces. Reconditioning/rewetting of each lens material with CLEAR CARE PLUS was described as having been attained when: 1) the contact angle of a treated lens after equilibration in saline was \leq the contact angle of the same lens out of pack or 2) when the contact angle of a lens treated with CLEAR CARE PLUS was $<$ the contact angle of the same lens after overnight equilibration in saline. BIOFINITY[†], FREQUENCY 55, ACUVUE OASYS[†] and PROCLEAR[†] lenses equilibrated in saline overnight resulted in statistically higher contact angle measurements compared to measurements following removal from the respective contact lens packaging saline solutions and exposure to air for a total of 90 seconds. For PUREVISION lenses, all conditions were statistically different from one another; however, treatment in CLEAR CARE PLUS resulted in the most improved wetting. Overall, treatment with CLEAR CARE PLUS provided a statistically significant lower wetting angle compared to overnight equilibration in saline for all lens materials evaluated except BOSTON XO[†] (RGP lenses).

Similarly, a study was conducted to evaluate wetting substantivity of CLEAR CARE PLUS with various lens materials. , i.e., SOFLENS[†] 38, PROCLEAR, FREQUENCY 55, BOSTON XO, ACUVUE OASYS, PUREVISION and BIOFINITY lenses. Lenses were evaluated for wetting via sessile drop contact angle measurements following various UNISOL*/air exposure intervals. Maintenance of lower contact angles for contact lens materials cycled in CLEAR CARE PLUS during the lens treatment regimen relative to the same contact lens material cycled in CLEAR CARE over time demonstrated that CLEAR CARE PLUS provided an improvement in wetting substantivity. Results from this study support that all lens materials following 10X UNISOL cycling/air exposure conditions were shown to have statistically significantly different means; lenses treated in CLEAR CARE PLUS were associated with the lower of the two contact angle measurements compared to CLEAR CARE. This was the case for all lens materials except for BOSTON XO (RGP lenses). Overall, CLEAR CARE PLUS provided an improvement in wetting substantivity for all lens materials evaluated except BOSTON XO, as evidenced by the p-values following multiple UNISOL/air exposure cycles.

Lubricity

A study was designed to characterize the interaction of EO₁₀BO₅ in the CLEAR CARE PLUS formulation with the surface chemistry of various contact lens materials to provide supporting evidence of EOBO's mechanism of action. Representative lenses from Group I, Group IV, SiHy and RGP lenses were evaluated via X-ray photoelectron spectroscopy (XPS) and colloidal probe atomic force microscopy (AFM).

XPS was employed in obtaining the percentage of elements on the upper 1-10 nm depth of the contact lenses creditable to adsorption/absorption of EO₁₀BO₅ in CLEAR CARE PLUS. The XPS data from the experiments in this study clearly demonstrate the ability of EO₁₀BO₅ in CLEAR CARE PLUS to interact with the various lens surfaces of the materials studied here, except for the Biofinity lens material which did not show a measurable amount of EO₁₀BO₅

adsorption/absorption. These measurable XPS spectra demonstrate that $\text{EO}_{10}\text{BO}_5$ is interacting and embedding itself on the surfaces of the lenses evaluated.

AFM was used in evaluating potential changes in coefficient of friction (CoF) between test lenses exposed to CLEAR CARE PLUS and control lenses. The results obtained indicate that for the SiHy lens materials, the CoF measured in this system decreased following exposure to CLEAR CARE PLUS.

These data support that, for SiHy lenses, $\text{EO}_{10}\text{BO}_5$ was present in amounts sufficient enough to impact reduction in friction as measured by colloidal probe AFM.

MICROBIOLOGY

Please refer to the DETAILED PHARMACOLOGY section.

TOXICOLOGY

The preclinical safety evaluation of CLEAR CARE PLUS included single-dose oral toxicity, repeat-dose ocular irritation, genotoxicity, cytotoxicity and sensitization studies. Carcinogenicity and reproductive/developmental toxicity studies were judged to be unnecessary, given the indicated usage, limited potential for systemic exposure, safety of predicate products, and preponderance of negative results in other toxicology evaluations. Since it was demonstrated that $\text{EO}_{10}\text{BO}_5$ had a low molar extinction coefficient in natural sunlight, further photosafety testing was not necessary, per ICH guidance. Safety assessment of impurities was based on the similarity to the predicate product and detailed evaluation of the only new excipient, $\text{EO}_{10}\text{BO}_5$. All pivotal toxicology studies were conducted in accordance with US FDA Good Laboratory Practice regulations and applicable ISO standards.

A single-dose (oral gavage) toxicity study in rats with neutralized CLEAR CARE PLUS, using a single dose of 20 mL/kg body, was conducted to evaluate toxicity as a result of accidental or intentional oral ingestion. No body weight changes and no clinical signs indicative of toxicity were observed.

Repeat-dose topical ocular studies were designed to evaluate the ocular irritation and toxicity potential of CLEAR CARE PLUS when used as a cleaning and disinfecting solution with representative contact lenses. Three repeat-dose ocular studies were conducted in New Zealand White rabbits, using soft or rigid gas permeable contact lenses treated daily in the CLEAR CARE PLUS clinical lens care regimen. Representative soft (traditional hydrogel) contact lenses from lens Groups I and IV were evaluated. Additionally, four silicone hydrogel lenses were evaluated as were two rigid gas permeable lenses. Studies were twenty-two days in length and were conducted with CLEAR CARE PLUS formulated at the highest end-of-shelf-life specifications for hydrogen peroxide (3.6%). CLEAR CARE PLUS was used to clean, disinfect and store the contact lenses one time prior to the first day of dosing and then following each daily lens wear period. Lenses were removed from the solution and inserted directly onto the eye, without a rinse. Contact lenses were worn on the right eye for an intended eight hour daily wear time on Study Days 1-21 and an intended wear time of four hours on Study Day 22. SENSITIVE EYES[†] Rewetting Drops (for traditional hydrogel and silicone hydrogel contact lenses) or OPTI-FREE^{*} REPLENISH^{*} Rewetting Drops (for rigid gas permeable contact lenses)

were administered to the contact lens bearing eye at two, four, and six hours post lens insertion for all groups to optimize retention (only at two hours post insertion on Study Day 22). Samples of CLEAR CARE PLUS stored at accelerated conditions (40°C, <25% RH, 28 weeks) were also evaluated in a three-day, repeat-dose rabbit ocular irritation study in order to evaluate safety at simulated extended shelf-life conditions. No test article-related adverse effects were observed in any of the studies.

Two *in vitro* genotoxicity assays (bacterial and mammalian) were conducted. Neutralized CLEAR CARE PLUS was used at doses of 1-100 µL/plate in the bacterial reverse mutation assay, and at doses of 10-100 µL/mL in the forward mutation. No mutagenic or genotoxic potential was observed.

CLEAR CARE PLUS was evaluated in the Guinea Pig Maximization test. The neutralized formulation was tested undiluted at doses of 0.1 mL intradermally and 0.3 mL topically and showed no evidence of causing delayed dermal contact sensitization.

The cytotoxicity potential of neutralized CLEAR CARE PLUS was evaluated in four cytotoxicity assays, with solution alone and in conjunction with contact lenses. Representative soft (traditional hydrogel) contact lenses from lens Groups I and IV were evaluated. Additionally, four silicone hydrogel lenses were evaluated as were two rigid gas permeable lenses. The agar overlay test was conducted with undiluted neutralized solution on a filter disc and the MEM Elution test was conducted with a 25% concentration (in medium). The Direct Contact and MTT cytotoxicity tests were conducted using contact lenses that were prepared under exaggerated conditions of soaking in 10 mL for 96 hours (four times longer than the usual practice of overnight disinfection). CLEAR CARE PLUS was negative for cytotoxicity in the agar overlay, elution and direct contact tests. CLEAR CARE PLUS was also negative for cytotoxicity at all extract concentrations and for all lens types in the MTT test, except for ACUVUE[®] 2 lenses (etafilcon A) at a 100% concentration. At this concentration, cell viability was slightly below the passing criteria of the test (67% as compared to the passing criteria of ≥ 70%). All other concentrations (12.5-50%) tested with ACUVUE 2 lenses were non-cytotoxic. Considering that the 100% extract concentration represents an exaggerated exposure, and given the weight of evidence of preclinical *in vivo* testing, other cytotoxicity tests, and clinical safety experience that showed no adverse ocular effects, the results of the MTT cytotoxicity testing with ACUVUE 2 lenses soaked in CLEAR CARE PLUS do not indicate a significant risk to the patient.

REFERENCES

Not applicable

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR PRODUCT
PATIENT INFORMATION**

**CLEAR CARE* PLUS Cleaning and Disinfecting Solution
3% Hydrogen Peroxide**

THIS PACKAGE INSERT CONTAINS IMPORTANT PRODUCT USE AND SAFETY INFORMATION. PLEASE READ CAREFULLY AND RETAIN FOR FUTURE REFERENCE.

Serious Warnings and Precautions

- **The red snap cap and dropper tip means that this product is NOT FOR DIRECT USE ON EYE.**
- **NEVER put CLEAR CARE PLUS into your eye OR onto a contact lens immediately before inserting the lens into your eye.** Lenses must be soaked in the provided lens case for at least 6 hours to neutralize the solution prior to wearing. OTHERWISE, BURNING AND STINGING WILL RESULT. If you accidentally insert a non-neutralized lens into your eye, remove it immediately and rinse the open eye with plenty of water or sterile saline for a few minutes. If burning or stinging continues, seek immediate assistance from an eye care professional before resuming contact lens wear.
- **NEVER clean or rinse your contact lenses in your hands with CLEAR CARE PLUS.** A mild, temporary skin discoloration (bleaching) of the fingers or hands may result from contact with non-neutralized solution. Always wash, rinse and dry your hands after exposure.

What is CLEAR CARE PLUS used for?

CLEAR CARE PLUS cleans, disinfects, neutralizes, removes protein and stores all types of contact lenses including silicone hydrogels.

How does CLEAR CARE PLUS work?

When used as directed, CLEAR CARE PLUS provides a unique cleaning action, which removes film and debris from the lens surface. CLEAR CARE PLUS also helps prevent serious eye infections by killing harmful microorganisms on contact lenses.

What are the ingredients in CLEAR CARE PLUS?

CLEAR CARE PLUS is a sterile, preservative-free, buffered aqueous solution containing 3% hydrogen peroxide (active), a wetting agent (HydraGlyde* Moisture Matrix [EOBO-21* – polyoxyethylene-polyoxybutylene], phosphonic acid (stabilizer), a cleaning agent poloxamer surfactant (PLURONIC[†] 17R4), purified water, sodium chloride (0.79%) as the tonicity agent, sodium phosphate (monobasic and dibasic salts for pH buffer). Sodium hydroxide or phosphoric acid is sometimes added to maintain proper pH balance. HydraGlyde* Moisture Matrix is a proprietary multi-functional block copolymer that is primarily designed for wetting and lubricating silicone hydrogel lenses.

CLEAR CARE PLUS comes in the following forms:

The CLEAR CARE PLUS Cleaning and Disinfecting Solution system consists of the CLEAR

CARE PLUS Cleaning and Disinfecting Solution and the special CLEAR CARE lens case (the lens case). The lens case consists of a transparent cup (the cup) and a connected unit of screw cap, lens holders (baskets) and the neutralizer catalyst disc attached at the bottom. CLEAR CARE PLUS and the special lens case must always be used together.

CLEAR CARE PLUS is supplied sterile in 90 mL, 360 mL and 480 mL sizes. The bottles are marked with lot numbers and expiration date. A new lens case is supplied with each purchase.

Do not use CLEAR CARE PLUS if:

- you are allergic to any of the ingredients;
- you use heat disinfection for your contact lenses.

Other warnings you should know about:

- For the product to work properly:
 - Only use the provided lens case with CLEAR CARE PLUS. Do not use a flat case. Do not use another solution with the provided lens case.
 - NEVER re-use solution in your lens case.
 - NEVER dilute or mix CLEAR CARE PLUS with any solution. Generic hydrogen peroxide may contain ingredients that have not been tested for eye safety and may discolor or damage your contact lenses.
- To avoid product contamination:
 - NEVER touch the open bottle tip to any surface.
 - NEVER transfer the solution to another container.
- NEVER allow your lenses to come into contact with non-sterile liquids, including tap water and saliva.
- NEVER clean your lenses with a separate cleaner immediately prior to using CLEAR CARE PLUS. Any left over cleaner on the lenses will result in foaming, potentially causing the solution to overflow from the lens case resulting in incomplete neutralization of the solution.
- Tell your eye care professional about all the medicines you take including any drugs, vitamins, minerals, natural supplements or alternative medicines. Some medications may affect contact lens wear.
- NEVER ingest CLEAR CARE PLUS, or gastric distress will result. If non-neutralized solution is ingested, immediately drink large amounts of water and seek medical assistance.
- Keep out of reach of children.

PROBLEMS WITH CONTACT LENSES AND LENS CARE PRODUCTS COULD RESULT IN SERIOUS INJURY TO YOUR EYE.

Follow your eye care professional's directions and all labeling instructions for proper use and care of your lenses and lens care products, including the lens case.

You should take the following precautions:

- Always wash, rinse and dry your hands before handling your lenses.
- Always use the new lens case provided with each purchase of CLEAR CARE PLUS.
- Do not use if the security seal around the bottle cap is broken or missing or if the bottle or lens case is damaged.
- Tightly close the snap cap on the bottle after each use.

- Discard any remaining solution 3 months after first opening.
- Never use the solution after expiry date.
- Always use the solution between 15°C and 30°C (59°F and 86°F) as neutralization below 15°C may take longer than 6 hours.
- Consult your eye care professional before changing lens care products.

How to Use CLEAR CARE PLUS:

Never put CLEAR CARE PLUS on your lenses and insert directly into your eye.

Otherwise, burning and stinging will result. If spillage occurs, clean up immediately with a paper towel. Wash, rinse and dry your hands before handling your lenses or touching your eyes.

1. Wash, rinse your hands and dry them with a clean towel.
2. Open the lens holder marked “L”. Remove your left lens and place it on the dome. Close the lens holder taking care to avoid damaging your lens.
3. Repeat the procedure with your right lens by placing it on the dome of the lens holder marked “R”.
4. Open the snap cap on the bottle of the CLEAR CARE PLUS and bend it back and out of the way.
5. Taking care not to splash yourself, thoroughly rinse the lenses in the lens holders with CLEAR CARE PLUS for 5 seconds.
6. Fill the CLEAR CARE cup to the fill line with CLEAR CARE PLUS. **DO NOT UNDERFILL OR OVERFILL.**
7. Place lens holders into the cup of the lens case and screw the cap closed. **DO NOT SHAKE THE LENS CASE.** Do not over tighten the lens case (only tighten finger tight).
8. Store the CLEAR CARE lens case upright.
 - If bubbles leak from the hole in the top of the lens case cap, non-neutralized CLEAR CARE PLUS solution may be present. Empty the solution from the lens case and thoroughly rinse the lens cup and lens holder with sterile saline or fresh CLEAR CARE PLUS. Clean up any spillage with a paper towel. Thoroughly wash, rinse and dry your hands before handling your lenses or touching your eyes. **REPEAT THE DISINFECTION PROCEDURE ABOVE.**
9. Allow lenses to soak for at least 6 hours to neutralize solution. You will see the bubbling action of 3% hydrogen peroxide working to kill microorganisms that can cause serious infections, and remove protein, dirt and build-up. After neutralization, no preservatives or harsh chemicals enter your eye. The disc neutralizes the active disinfectant to create a gentle saline solution close to your own tears.
10. After washing, rinsing and drying your hands, remove your lenses from lens holder.
11. Your lenses are now ready to wear.
12. Discard used solution, rinse the CLEAR CARE lens cup and lens holder with sterile saline or fresh CLEAR CARE PLUS - **DO NOT USE TAP WATER OR NON-STERILE WATER.**
13. Turn the lens holder upside down outside the cup and allow both to air dry.
14. If you do not intend to wear your lenses immediately after disinfection/neutralization, you may store them in the neutralized CLEAR CARE PLUS in the unopened CLEAR CARE lens case for up to 14 days. After this time, your lenses must be cleaned and disinfected with CLEAR CARE PLUS prior to wear. If recommended by your eye care professional: Rinse lenses before insertion with sterile saline.

What are possible side effects from using CLEAR CARE PLUS?

These are not all the possible side effects you may feel when using CLEAR CARE PLUS. If you experience persistent discomfort or irritation remove your lenses, stop using the product and consult your eye care professional. If you experience any side effects not listed here, contact your healthcare professional. Please also see Warnings and Precautions.

The following problems may occur with contact lens wear: eyes sting, burn or itch (irritation), comfort is less than when lens was first placed on the eye, feeling of something in the eye (foreign body, scratched area), excessive watering (tearing) of the eye, unusual eye secretions, redness of the eye, reduced sharpness of vision (poor visual acuity), blurred vision, rainbows or halos around objects, sensitivity to light (photophobia), or dry eyes.

If you notice any of the above, IMMEDIATELY remove your lenses.

- If the problem stops and the lenses appear to be undamaged, repeat the cleaning, disinfection and neutralization process and reinsert the lenses.
- If the lens is in any way damaged, do not put the lens back on your eye. Place the lens in the lens case and contact your eye care professional.
- If the lens has dirt, an eyelash, or other foreign body on it, repeat the cleaning, disinfection and neutralization process and reinsert the lens.
- If the problem continues, IMMEDIATELY remove the lens and consult your eye care professional.

If any of the above symptoms occur, a serious condition such as infection, corneal ulcer, neovascularization or iritis may be present. Eye problems can develop rapidly and lead to loss of vision. Seek immediate professional identification of the problem and prompt treatment to avoid serious eye damage.

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

3 ways to report:

- Online at [MedEffect](#);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
 - Fax to 1-866-678-6789 (toll-free), or
 - Mail to: Canada Vigilance Program

Health Canada, Postal Locator 0701E
Ottawa, ON
K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at [MedEffect](#).

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store below 30°C (86°F) and protect from light.

If you want more information about CLEAR CARE PLUS:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the [Health Canada website](#); the manufacturer's website www.alcon.ca, or by calling 1-800-613-2245.

This leaflet was prepared by Alcon Canada Inc.

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Last Revised December 11, 2015