

PRODUCT MONOGRAPH

**Biotrue™ multi-purpose solution**

Polyaminopropyl biguanide, 0.00013% w/v

Professed Standard

Polyquaternium-1, 0.0001% w/v

Professed Standard

Contact Lens Disinfectant

Sponsor:  
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1400 North Goodman Street  
Rochester, New York 14609  
USA

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Imported and distributed by:  
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## Table of Contents

<b>PART I: HEALTH PROFESSIONAL INFORMATION.....</b>	<b>2</b>
SUMMARY PRODUCT INFORMATION .....	2
INDICATIONS AND CLINICAL USE.....	2
CONTRAINDICATIONS .....	3
WARNINGS AND PRECAUTIONS.....	3
ADVERSE REACTIONS .....	3
DRUG INTERACTIONS.....	4
DOSAGE AND ADMINISTRATION.....	4
OVERDOSAGE .....	5
ACTION AND CLINICAL PHARMACOLOGY .....	5
STORAGE AND STABILITY.....	6
SPECIAL HANDLING INSTRUCTIONS .....	6
DOSAGE FORMS, COMPOSITION AND PACKAGING.....	6
<b>PART II: SCIENTIFIC INFORMATION.....</b>	<b>7</b>
PHARMACEUTICAL INFORMATION .....	7
CLINICAL TRIALS.....	8
DETAILED PHARMACOLOGY.....	9
TOXICOLOGY .....	12
REFERENCES .....	14
<b>PART III: CONSUMER INFORMATION .....</b>	<b>15</b>

### **Biotrue™ multi-purpose solution**

Polyaminopropyl biguanide and Polyquaternium-1

#### **PART I: HEALTH PROFESSIONAL INFORMATION**

##### **SUMMARY PRODUCT INFORMATION**

<b>Route of Administration</b>	<b>Dosage Form / Strength</b>	<b>Clinically Relevant Nonmedicinal Ingredients</b>
Contact Lens Disinfectant	polyaminopropyl biguanide (0.00013%) and polyquaternium-1 (0.0001%)	None <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

##### **INDICATIONS AND CLINICAL USE**

Biotrue™ multi-purpose solution is indicated for:

- use in the daily conditioning, cleaning, removal of protein deposits, rinsing, chemical (not heat) disinfection and

storage of soft (hydrophilic) contact lenses, including silicone hydrogel lenses, as recommended by your eye care professional.

**Pediatrics (< 18 years of age):** No data is available

## **CONTRAINDICATIONS**

- Biotrue™ multi-purpose solution should not be used by patients who are hypersensitive to this product 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.

## **WARNINGS AND PRECAUTIONS**

### **General**

**Problems with contact lenses and lens care products could result in corneal infection and/or ulcer and lead to loss of vision.**

**Failure to discard solution from lens case after each use or use of water to care for contact lenses may lead to contamination resulting in eye injury and potential loss of vision.**

It is important to advise Biotrue™ multi-purpose solution users to follow given directions and all labelling instructions for proper use of lenses and lens care products, including the lens case.

Eye problems, including corneal ulcers, can develop rapidly and lead to loss of vision. Daily wear lenses are not indicated for overnight wear and should not be worn while sleeping. Clinical studies have shown the risk of serious adverse reactions is increased when these lenses are worn overnight. Extended wear lenses should be regularly removed for cleaning and disinfection or for disposal and replacement on the schedule prescribed by your eye care professional. Clinical studies have shown that there is an increased incidence of serious adverse reactions in extended wear contact lens users as compared to daily wear contact lens users. Studies have also shown that the risk of serious adverse reactions increases the longer extended wear lenses are worn before removal for cleaning and disinfection or for disposal and replacement. Studies have also shown that smokers have a higher incidence of adverse reactions.

Biotrue™ multi-purpose solution users should be advised to remove their contact lenses immediately and contact their eye care professional if they experience eye discomfort, excessive tearing, vision changes or redness of the eye. It is recommended that contact lens wearers see their eye care professional twice each year or more frequently, if required.

Biotrue™ multi-purpose solution users should be advised to:

- Follow the complete recommended lens rubbing and rinsing times in the product labelling to adequately disinfect lenses and reduce the risk of contact lens contamination. Reduced rubbing or rinsing time may not adequately clean lenses.
- Never ‘top-off’ or re-use the solution.
- Not expose or store lenses in or rinse lens case with any water, such as tap, bottled or distilled, or with any non-sterile solution.
- Clean, rinse and air-dry the lens case each time lenses are removed.
- Replace lens case frequently.
- Not touch tip of container to any surface to avoid contamination.
- Keep the bottle tightly closed when not in use.
- Store the solution at room temperature.
- Discard any remaining solution 90 days after opening.
- Keep out of the reach of children.
- Not use with heat (thermal) disinfection.

## **ADVERSE REACTIONS**

## **Adverse Reaction Overview**

In general, the following problems may occur with use of contact lens solutions: 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.

## **Clinical Trial Adverse 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.*

In clinical studies, over 350 patients have used Biotrue™ multi-purpose solution for the daily cleaning and disinfection of soft contact lenses. There have been no adverse events reported for Biotrue™ multi-purpose solution.

## **Post-Market Adverse Reactions**

The product is only recently available in the United States. To date, there have been no reports of post-market adverse events.

## **INTERACTIONS**

### **Overview**

*In vitro* lens compatibility studies with Biotrue™ multi-purpose solution have shown that the lens care product is compatible with soft contact lenses from FDA Groups I, II and IV as well as silicone hydrogel lenses. Drug interaction studies with Biotrue™ multi-purpose solution and other ophthalmic solutions, either *in vivo* or *in vitro*, have not been performed.

Not for use with heat (thermal) disinfection.

## **DOSAGE AND ADMINISTRATION**

### **Recommended Dose and Dosage Adjustment**

To condition, clean, remove protein and disinfect lenses, complete these simple steps. This daily regimen is recommended by Bausch & Lomb, Inc. for a healthy and comfortable contact lens wearing experience:

**Step 1:** Place at least 3 drops of Biotrue™ multi-purpose solution on each side of lens surface and gently rub for 20 seconds.

**STEP 2:** Thoroughly rinse each side of the lens for 5 seconds with Biotrue™ multi-purpose solution.

**STEP 3:** Place cleaned contact lenses in the lens case and fill with fresh Biotrue™ multi-purpose solution. Soak at least 4 hours. Remember to always use fresh solution – discard solution from lens case after each use.

The lenses are now ready to wear. If any debris remains on contact lenses, rinse with Biotrue™ multi-purpose solution prior to insertion.

Based upon individual tear chemistry and lens-wearing schedule, eye care professionals may recommend additional products or procedures.

Contact lenses are to be stored in Biotrue™ multi-purpose solution in a closed lens case if not worn immediately after cleaning. Contact lenses should not be stored in simple saline in place of Biotrue™ multi-purpose solution. Saline solution will not disinfect.

Contact lenses may be stored in an unopened case until ready to wear, up to a maximum of 30 days. If lenses are stored for longer periods of time, they must be cleaned and disinfected with fresh Biotrue™ multi-purpose solution every 30 days and prior to lens insertion.

## **OVERDOSAGE**

Not Applicable.

## **ACTION AND CLINICAL PHARMACOLOGY**

### **Mechanism of Action**

When used daily, Biotrue™ multi-purpose solution dissolves protein and cleans, loosens and removes accumulations of film, debris and deposits from soft contact lenses. Biotrue™ multi-purpose solution helps prevent the formation of irritating deposits on the lens surface. It kills harmful microorganisms on the lens. While your lens is soaking, the formula envelops the lens in a moisture-rich cushion to help the lens remain comfortable throughout the day. Biotrue™ multi-purpose solution can also be used to rinse lenses.

**Biotrue Benefits:** Biotrue™ multi-purpose solution incorporates a lubricant also found in your eyes, and is balanced to match the pH of healthy tears. Biotrue™ multi-purpose solution cushions and rehydrates lenses for comfortable wear. Biotrue™ multi-purpose solution helps prevent certain tear proteins from denaturing for clean lenses and inhibits the formation of deposits that can cause discomfort and can shorten lens wearing time. Clinical results demonstrated that for comfort-related symptoms/complaints, such as Comfort over the 3-month follow-up period, average daily wear time, lens characteristics, rewetting drop use, visual acuity by LogMAR score as well as subject and investigator assessments and preferences, were generally the same, showing that Biotrue™ multi-purpose solution in a rub regimen provided a continuous level of comfort. By keeping lenses hydrated and clean, Biotrue™ multi-purpose solution makes wearing contact lenses comfortable all day.

## **STORAGE AND STABILITY**

Biotrue™ multi-purpose solution should be stored at room temperature. Lenses may be stored up to a maximum of 30 days in an unopened lens case. Lens may be stored for longer but must be cleaned and disinfected with fresh Biotrue™ multi-purpose solution every 30 days prior to lens insertion.

## **SPECIAL HANDLING INSTRUCTIONS**

Contact lens wearer should be advised to:

- Always wash and rinse hands before handling their contact lenses.
- Clean, rinse and disinfect their lenses each time they are removed.
- Always handle the same lens, the right or the left, first in order to avoid mix-ups.
- After use, always empty and rinse the lens case with fresh Biotrue™ multi-purpose solution, and allow to air dry.
- Avoid contamination by not touching the tip of the Biotrue™ multi-purpose solution container to any surface and replace the cap after using.
- Not use Biotrue™ multi-purpose solution with heat (thermal) disinfection.
- Never re-use the solution.
- Keep the bottle tightly closed when not in use.

## **DOSAGE FORMS, COMPOSITION AND PACKAGING**

Biotrue™ multi-purpose solution is a sterile, isotonic solution that contains hyaluronan, sulfobetaine, poloxamine, boric acid, sodium borate, edetate disodium and sodium chloride and preserved with a dual disinfection system (polyaminopropyl biguanide 0.00013% w/v and polyquaternium 0.0001% w/v).

Biotrue™ multi-purpose solution is available in sterile 60 mL, 120 mL, 240 mL, 300 mL, and 480 mL PET bottles. Bottles and cartons are marked with a lot number and expiration date.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

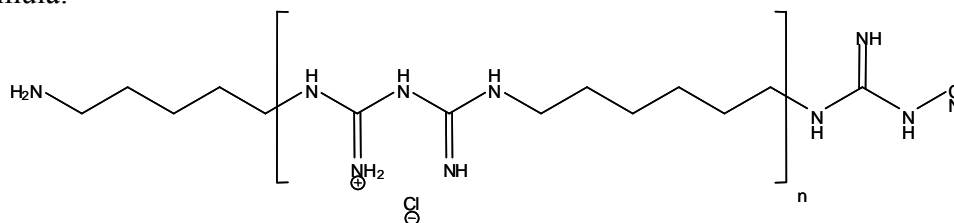
#### Drug Substance 1

Proper name: Polyaminopropyl Biguanide Hydrochloride Solution, 20% w/w

Chemical name: Poly(iminocarbonimidoyliminocarbonimidoylimino-1,6-hexanediyl) hydrochloride

Molecular formula and molecular mass:  $(C_8H_{17}N_5)_n \cdot x HCl$   
6,000 to 25,000 daltons (based on the acceptance criterion)

Structural formula:



Physicochemical properties:

Parameter	Results
Physical appearance	Clear, colourless to yellowish liquid
Solubility	Freely soluble in water
pH	The pH of the 20% w/w solution is 5.0 – 6.0.

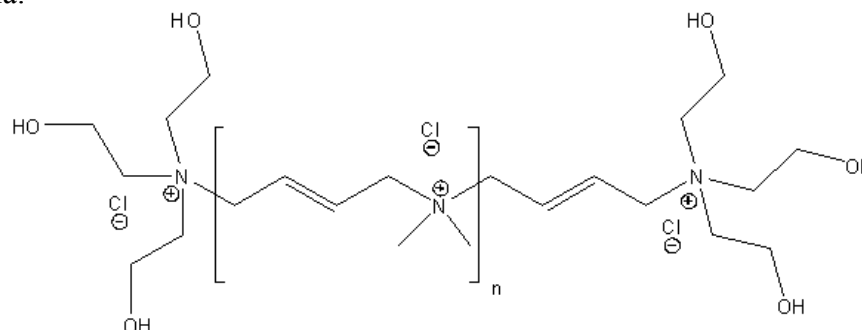
#### Drug Substance 2

Proper name: Polyquaternium-1, 35% w/w Solution

Chemical name: 1) Poly[(dimethyliminio)-2-butene-1,4-diyl chloride],  $\alpha$ -[4-[tris(2-hydroxyethyl)ammonio]-2-butenyl]- $\omega$ -[tris(2-hydroxyethyl)ammonio]-, dichloride  
2)  $\alpha$ -[(E)-4-[Tris(2-hydroxyethyl)ammonio]-2-butenyl]- $\omega$ -[tris(2-hydroxyethyl)ammonio]-poly[(dimethyliminio)(E)-2-butenylene]chloride]dichloride

Molecular formula and molecular mass:  $(C_6H_{12}ClN)_n \bullet C_{16}H_{36}Cl_2N_2O_6$   
6000 – 30000 (based on the acceptance criterion)

Structural formula:



Physicochemical properties:

Parameter	Results
Physical appearance	Clear, amber to dark brown liquid
Solubility	Freely soluble in water
pH	The pH of the 35% w/w solution is 6.0 – 8.0.

## CLINICAL TRIALS

### Study demographics and trial design

**Table 1- Summary of patient demographics for the clinical trial with Biotrue™ multi-purpose solution**

Study #	Trial design	Dosage, route of administration and duration	Study subjects-Enrolled/Eligible/Completed (n=number)	Mean age (Range)	Gender M/F (eligible study subjects)
1	Randomized, controlled	Daily lens cleaning of soft contact lenses for 3 months	541 / 535 / 484		152/383
		Biotrue™ multi-purpose solution (rub regimen)	179 / 178 / 165	33.6 (18-66)	54/124
		Biotrue™ multi-purpose solution (no rub regimen)	179 / 176 / 156	32.8 (18-66)	43/133
		AQuify® Multi-Purpose Solution (rub regimen)	183 / 181 / 163	32.9 (18-59)	55/126

One pivotal trial was conducted to compare the safety and efficacy of Biotrue™ multi-purpose solution to a commercially available lens solution when used on a daily basis by adapted wearers of silicone hydrogel or Group IV contact lenses. Study 1 was a 3-month randomized, controlled study. Subjects were dispensed a study solution according to unique randomization tables supplied to each Investigator, as well as one pair of their habitual lenses. For 3 months, lenses were to be worn on a daily wear basis (with scheduled replacement at the 1-Month and 2-Month Follow-Up Visits) and cleaned and disinfected at the end of each day according to the instructions provided with the study solution dispensed. One third of the subjects were to follow a no-rub regimen using Biotrue™ multi-purpose solution (Test A), another third a rub regimen (3 drops on each side of lens and rub for at least 10 seconds) with the Biotrue™ multi-purpose solution (Test B) and the last third a rub regimen with Control solution (same procedure as for Biotrue™ rub regimen). The soaking/cleaning time for all groups was a minimum of 4 hours. No saline rinse was necessary and subjects were to rinse the lenses with the solution if any debris remained on the lenses prior to lens placement. Subject participation in the study was approximately 3 months, with follow-up visits at 2 weeks, 1 month, 2 months, and 3 months.

### Study results

The primary safety endpoint for the pivotal study was the occurrence of graded slit lamp scores greater than 2. The primary efficacy endpoints were subject symptoms/complaints regarding various qualities of the lenses and assigned study solutions as well as the type and overall occurrence of clinically significant lens deposits. Additionally, lens deposits were classified by type of deposit, degree and percent coverage. Analyses were performed at the Initial, 2-Week, 1-Month, 2-Month, 3-Month visits as well as overall. The principal goal of the statistical analyses of the primary endpoints was to determine if Biotrue multi-purpose solution (Test A and B) was non-inferior to the Control solution.

For the primary safety endpoint, Biotrue™ multi-purpose solution in a rub regimen (Test B) was found to be non-inferior to the Control at all follow-up visits for slit lamp findings greater than Grade 2. The safety of Biotrue™



multi-purpose solution was also supported by the following measurements: visual acuities, keratometry and spherocylindrical refraction between baseline and exit visits. It was concluded that Biotrue™ multi-purpose solution was safe for use with soft contact lenses in a rub regimen.

For the first primary efficacy end point, symptoms/complaints ratings demonstrated that Biotrue™ multi-purpose solution was non inferior to Control. Results for comfort-related symptoms/complaints, such as Comfort over the 3-month follow-up period, average daily wear time, lens characteristics, rewetting drop use, visual acuity by LogMAR score as well as subject and investigator assessments and preferences, were generally the same, showing that Biotrue™ multi-purpose solution in a rub regimen provided a continuous level of comfort.

Although the second efficacy endpoint, subjective on-eye deposit profiles between Biotrue™ multi-purpose solution in a rub regimen and Control, showed some differences, the objective digital image analysis of deposits and subject assessments showed that the product was effective. Subject assessments highlighting product experiences for performance qualities such as comfort, cleanliness, and moisture retention are effectiveness attributes associated with use of Biotrue™ multi-purpose solution in a rub regimen.

## **DETAILED PHARMACOLOGY**

### Disinfection Efficacy Testing

Extensive microbiological testing of Biotrue™ multi-purpose solution was conducted to assess its disinfection efficacy. Testing was performed in accordance with the ISO/FDA Stand Alone Procedure for Disinfecting Products. All the testing performed used Biotrue™ multi-purpose solution on three different challenge organism preparations. The challenge organism preparations contained the same organisms (*Staphylococcus aureus* ATCC 6538, *Pseudomonas aeruginosa* ATCC 9027, *Serratia marcescens* ATCC 13880, *Candida albicans* ATCC 10231 and *Fusarium solani* ATCC 36031) but at varying relative concentrations. The formulation was evaluated with and without organic soil and at various concentrations of disinfectants (dose-response study). Organic soil consisted of approximately  $10^7$  colony forming units (CFU)/mL of heat killed *Saccharomyces cerevisiae* cells resuspended in fetal bovine serum. The formulation consistently exceeded the ISO primary acceptance criteria even when the concentration of the disinfectants was lowered to 40% of the labelled concentration (0.52 ppm PAPB and 0.4 ppm PQ-1).

The ISO/FDA Regimen Procedure for Disinfecting Regimens was performed in five separate studies to demonstrate the contact lens disinfecting efficacy of Biotrue™ multi-purpose solution. All contact lenses were inoculated with challenge organisms suspended in FDA organic soil. The rub regimen consisted of a five-second rub per lens side with a multi-purpose solution, a five-second rinse per lens side followed by a 4-hour disinfecting soak. For the no-rub regimen, the same procedure was followed except no rub was performed. The no-rub regimen is considered the worst case scenario and represents consumer non-compliance. Following the soak, the lenses and solution were evaluated for surviving challenge organisms. The methodology used to evaluate the test solution in regimen is compliant to the methods noted in ISO Standard 14729 and the FDA Premarket Notification (510(k)) Guidance Document for Contact Lens Care Products.

Biotrue™ multi-purpose solution as well as Biotrue™ multi-purpose solution formulated at the lower stability specifications with the ISO Regimen Procedure as a rub and no-rub regimen with organic soil was evaluated. The formulations met or exceeded the ISO acceptance criteria as both a rub and no-rub regimen.

The disinfecting efficacy of Biotrue™ multi-purpose solution and Biotrue™ multi-purpose solution formulated at the lower stability specifications was also determined after soak intervals of 4 hours, 7 days, 14 days, 21 days and 30 days. It was found that the FDA/ISO performance criteria were met when used in a no-rub regimen with both formulations.

When Biotrue™ multi-purpose solution was compared to 3 commercially available multi-purpose solutions,

Biotrue™ multi-purpose solution performed equivalently to or better than the other marketed multi-purpose solutions when tested with five types of marketed soft contact lenses.

Stand alone and regimen disinfection efficacy studies were conducted with Biotrue™ multi-purpose solution at the initial stability interval and a stand alone study with soil is ongoing and will be examined up to 36 months at two temperature conditions (25°C and 30°C). Additional testing at accelerated temperatures (40°C) for up to 9 months was conducted. Refer to 3.2.P.8.1 Stability Summary and Conclusions for stability testing. Acceptance criteria were met for all studies. Data is available for 9 months of storage at 40°C/20%RH, 12 months storage at 25°C/40%RH, and 13 months storage at 30°C/65%RH so far. The results of the stability evaluations at the 3 temperatures demonstrate that Biotrue™ multi-purpose solution in 2 oz.

(60 mL) PET 9921 containers met the ISO 14729/FDA Stand Alone Procedure for Disinfecting Products using a four (4) hour disinfection time, and incorporating organic soil with the challenge organism preparations.

### Lens Cleaning

**Critical Micelle Concentration:** Cleaning efficacy has been demonstrated by the evaluation of the Critical Micelle Concentration (CMC) of poloxamine 1107 and sulfobetaine contained in Biotrue™ multi-purpose solution and the surface tension of Biotrue™ multi-purpose solution itself. The surface tension of Biotrue™ multi-purpose solution was determined to be  $44.3 \pm 0.4$  dynes/cm; the CMC of poloxamine 1107 in the presence and absence of sulfobetaine was determined to be 0.29% w/w and 0.0045% w/w, respectively. The surfactant concentration is well above the CMC calculated here.

**Protein Removal Study:** In an *in vitro* cleaning study, lysozyme was deposited on Group I, Group II, Group IV and four (4) silicone hydrogel lenses. The lenses were subject to one no-rub disinfection cycle with one of three multipurpose solutions and the lysozyme remaining on the lenses quantified with an HPLC assay. Considering all lens materials tested, Biotrue™ multi-purpose solution demonstrated the ability to remove lysozyme deposits from contact lenses that was either superior to, or equivalent to comparator multi-purpose solutions.

**Protein Stabilization:** In investigating protein stabilization, the lysozyme activity assays conducted provide mechanistic evidence that Biotrue™ multi-purpose solution has the ability to stabilize lysozyme under conditions that typically denature lysozyme and, thereby, potentially prevents the build-up of problematic denatured protein deposits on contact lenses. Both Biotrue™ multi-purpose solution and ReNu MultiPlus® Multipurpose Solution demonstrated statistically greater ability to stabilize lysozyme, as demonstrated by its activity retention, than other comparator multi-purpose solutions or phosphate buffered saline control.

**Clinical Returned Lenses:** Bausch & Lomb, Inc. collected lenses (silicone hydrogel and Group IV) from subjects that had been worn for one month during Clinical Study 554. The lens deposits were measured *ex vivo* using an image analysis system with NIH Image v1.46 software. Results of the quantitative digital image analysis demonstrated that there were no statistical differences between each of the Test group lenses (Biotrue™ multi-purpose solution No-Rub Regimen and Biotrue™ multi-purpose solution Rub Regimen) compared to the Control lenses (AQuify® Multi-Purpose Solution Rub Regimen) with respect to mean density and percent coverage of deposits over all lenses.

### Comfort Agent Assessment

Bausch & Lomb, Inc. evaluated the effect of Biotrue™ multi-purpose solution has on the contact angle for Group I, Group II, Group IV and four (4) silicone hydrogel lenses. After lenses were prepared for the study, they were soaked for 24 hours in Biotrue™ multi-purpose solution. The wetting angle was determined immediately after the soak step and after water was dripped on the lens surface for 1.5 hours, 3 hours and overnight to simulate the effect of tears during lens wear. A statistically significant reduction in average contact angle was observed for each of the lens types immediately after being soaked in Biotrue™ multi-purpose solution as well as after 1.5 hours of dripping. A reduction in the average contact angle of Acuvue 2, Acuvue ADVANCE, and Biofinity lenses was observed after 3 hours of dripping. After being dripped on overnight, Acuvue 2 and Biofinity lenses still had a lower average contact angle than the control lens.

The presence of hyaluronan on the lens surface after soaking in Biotrue™ multi-purpose solution was demonstrated through confocal microscopy of lenses soaked in Biotrue™ multi-purpose solution formulated with fluorescein labelled hyaluronan (qualitative measurement) and spectrophotometric evaluation of lenses stained with Alcianblue

stain (quantitative measurement). Each experiment was conducted with Group I, Group II, Group IV and five (5) silicone hydrogel lenses.

Two separate experiments evaluated the release of either fluorescein labelled hyaluronan or sulfobetaine and poloxamine 1107 from Group I, Group II, Group IV and six (6) silicone hydrogel lenses after soaking overnight in Biotrue™ multi-purpose solution. The quantity of hyaluronan was measured using a Microplate Fluorescence Reader, while the amount of sulfobetaine and poloxamine 1107 were measured indirectly by comparing the surface tension of the solution at the start of the experiment to intervals over a 12 hour period. Saline solution was dripped on the lenses to simulate the effect of tears during lens wear and collected hourly over a 12-hour period. Hyaluronan, sulfobetaine and poloxamine 1107 continued to be released from the lenses for at least 12 hours. An additional study was performed to evaluate the rate of release of hyaluronate over a 20 hour time period. Hyaluronan continued to be released from the lenses for at least 20 hours. The in vitro performance of Biotrue™ multi-purpose solution suggests it may contribute to lens conditioning for up to 20 hours. The clinical significance of the study results has not been established.

In an effort to show that hyaluronan persistence on the lens would possibly reduce end-of-day dryness and long lasting comfort, a further study was performed to compare the amount of hyaluronan that is released from a contact lens soaked for 5 minutes in lens rewetting drop solution to lenses soaked for 4 hours to overnight in Biotrue™ multi-purpose solution. Hyaluronan, a conditioning agent in lens rewetting drop solutions, was adsorbed on all traditional and silicone hydrogel contact lenses tested upon soaking for five minutes. Hyaluronan was released from the lenses throughout at least a seven (7) hour time period when rinsed with Hanks' Balanced Salt Solution at a rate mimicking tear secretions. It was found that although the effect varied by lens material, similar amounts of hyaluronan were adsorbed to the lens surface and released from the lenses when they were soaked overnight in Biotrue™ multi-purpose solution as compared to lenses soaked for five (5) minutes in the simulated lens rewetting drops.

#### Preservative Efficacy

Additional Preservative Efficacy evaluations showed that Biotrue™ multi-purpose solution and Biotrue™ multi-purpose solution formulated at the lower stability limits exceeds the requirements of the FDA and ISO 14730 Standard at the initial stability time point. Therefore, the product is considered adequately preserved. A 90-day discard date after the opening of Biotrue™ multi-purpose solution was also established according to ISO 14730 Standard.

#### Photostability

Photostability testing of the product was conducted in accordance with ICH Q1B *Photostability Testing of New Drug Substances and Products*. Test samples of 2 oz Biotrue™ multi-purpose solution in clear PET bottles received full exposure to white fluorescent light followed by exposure of near ultra-violet fluorescent light for approximately 7 days. The results of the evaluation demonstrate there is no difference in the physical, chemical, and microbiological properties of Biotrue™ multi-purpose solution stored under photostability conditions and stored for 3 months at 25°C/40% RH.

#### Lens Compatibility

The lens compatibility of Biotrue™ multi-purpose solution was determined after FDA Groups I, II and IV and silicone hydrogel contact lenses had been cycled 30 times according to the proposed regimen based on FDA Premarket Notification (510(k)) Guidance Document for Contact Lens Care Products and ISO 11981 for lens-solution compatibility. The average changes for each parameter (diameter, base curve, center thickness, power and refractive index) were measured before and after cycling. Cosmetic evaluations were also completed. The results indicated that Biotrue™ multi-purpose solution is compatible with soft contact lenses test.

## **TOXICOLOGY**

A number of toxicity studies have been performed with Biotrue™ multi-purpose solution and packaging components including: acute dose; ocular irritation; local tolerance; cytotoxicity and systemic toxicity. All toxicology studies

were conducted under GLP conditions.

The acute dose toxicity was evaluated in rats using a single 15g/kg of body weight oral (gavage) dose of the undiluted Biotrue™ multi-purpose solution. Generally, all animals appeared normal throughout the study and the gross necropsy examination revealed no test material-related lesions. It was concluded that for male and female rats Biotrue™ multi-purpose solution was not considered toxic at a dose of 15 g/kg by the oral route in the rat.

A series of *in vivo* ocular irritation studies were completed with Biotrue™ multi-purpose solution accordance with ISO 10993–Part 10 Standard. The first group of studies evaluated the potential of Biotrue™ multi-purpose solution and Biotrue™ multi-purpose solution formulated at the upper limit of the product specification to produce irritation following a single instillation to the ocular tissue of a rabbit. Ocular reactions evaluated at 1, 24, 48 and 72 hours after the single exposure revealed no ocular irritation.

Similar ocular irritation studies were also performed as above on seven commercial brands of soft contact lenses available in Canada cycled 30 times in Biotrue™ multi-purpose solution and Biotrue™ multi-purpose solution formulated at the upper limit of the product specification for a minimum of 4 hours for each cycle. The purpose of these studies was to evaluate the potential for leachables extracted either with 0.9% sodium chloride or with sesame oil from the cycled lenses to produce irritation following a single instillation to the ocular tissue of the rabbit. It was found that all seven brands tested did not produce any evidence of significant ocular irritation in the treated eyes as compared to the untreated control eyes.

Two ocular irritation studies were performed to evaluate the potential for leachables extracted from the plastic packaging material used for Biotrue™ multi-purpose solution in accordance with ISO 10993-10. Neither the 10 oz. PET bottles nor the Snap Caps produced any evidence of significant ocular irritation in the treated eyes as compared to the untreated.

*In vivo* ocular compatibility studies were performed in accordance with ISO 9394 Standard. The study was performed on 5 commercial brands of contact lenses available in Canada treated nightly with either Biotrue™ multi-purpose solution, or a competitor product. The purpose of these studies was to evaluate the potential for lenses maintained with the test solution to produce irritation to the ocular tissue of rabbits in a simulated use study for 22 days. It was found that there were no ocular irritation trends that would be considered clinically significant, microscopically the ocular tissue of the test and control eyes were similar and essentially normal and in corneal lactic acid analysis, the lenses treated with Biotrue™ multi-purpose solution had no clinical effect on oxygen transport or corneal metabolism.

Delayed contact sensitization studies were performed in accordance to ISO 10993-Part 10 Standard on Biotrue™ multi-purpose solution and on seven commercial brands of soft contact lenses available in Canada soaked in the multi-purpose solution. The murine local lymph node assay (LLNA) was used to determine the potential for the test solution to cause sensitization. The sensitization reaction was measured by assessing the level of lymphocyte proliferation within the lymph nodes adjacent to the treatment site. In the murine LLNA, an increase in proliferation of lymphocytes in the lymph nodes draining the ears is an indication of sensitization. It was found that Biotrue™ multi-purpose solution and the 7 brands of contact lenses soaked in the solution were not considered a sensitizing agent.

*In vitro* cytotoxicity testing based on the requirements of the FDA guidance document for contact lens care products and ISO 10993-Part 5 Standard was conducted on Biotrue™ multi-purpose solution. Results from the seven studies soaking lenses for 96 hours showed that regardless of lens type (Lotrafilcon B, Balafilcon A, Polymacon, Alphafilcon A, Etafilcon A, Galyfilcon A or Comfilcon A lenses), the test solution was not cytotoxic.

An agar diffusion cytotoxicity study based on the USP guidelines and ISO 10993-Part 5 Standard was conducted with Biotrue™ multi-purpose solution. There were no measurable zones of lysis around or under the treated filter paper discs. It was concluded that Biotrue™ multi-purpose solution was not considered cytotoxic.

Similar studies were performed to evaluate the potential for leachables extracted from the packaging materials (PET

bottles and Snap Caps) to produce a cytotoxic response. The extracts were placed directly on the monolayer of cells. Extracts made from the packaging materials showed no evidence of causing cell lysis or toxicity.

Studies were also performed to evaluate the potential for leachables extracted from the packaging materials (PET bottles and Snap Cap) to produce a systemic toxicity response. Extracts for both the packaging materials were prepared using Sodium Chloride (SC) or Sesame Seed Oil (SO). The SC extracts were injected intravenously and the SO extracts were intraperitoneal injections. Under the conditions of these studies, the test articles, both the Snap Caps and PET bottles, showed no evidence of systemic toxicity.

## **REFERENCES**

1. Schein OD and Poggio EC. Ulcerative Keratitis in Contact Lens Wearers. *Cornea* 1990; 9 (Suppl. 1):S55-S58
2. Study 1: Phase III Safety and Efficacy Study. Internal Report. Bausch & Lomb, Inc.

## PART III: CONSUMER INFORMATION

### BIOTRUE™ multi-purpose solution

polyaminopropyl biguanide 0.00013% w/v  
and  
polyquaternium-1 0.0001% w/v

This leaflet is part III of a three-part "Product Monograph" published when Biotrue™ multi-purpose solution was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Biotrue™ multi-purpose solution. Contact your eye care professional or pharmacist if you have any questions about the product.

#### ABOUT THIS PRODUCT

##### **What the product is used for:**

Biotrue™ multi-purpose solution is indicated for use in the daily conditioning, cleaning, removal of protein deposits, rinsing, chemical (not heat) disinfection and storage of soft (hydrophilic) contact lenses, including silicone hydrogel lenses, as recommended by your eye care professional.

##### **What it does:**

When used daily, Biotrue™ multi-purpose solution:

- Helps prevent the formation of irritating deposits on the lens surface.
- Dissolves protein and cleans, loosens and removes debris and deposits from lenses.
- Kills harmful microorganisms (germs) on the lens.
- Envelops the lens in a moisture-rich cushion while your lens is soaking to help the lens remain comfortable throughout the day.
- Is used to rinse and store lenses.

##### **When it should not be used:**

If you are allergic to any ingredient in this product, do not use.  
(see What the other important ingredients are)

##### **What the active ingredients are:**

polyaminopropyl biguanide and polyquaternium-1

##### **What the other important ingredients are:**

Biotrue™ multi-purpose solution is a sterile, isotonic solution that contains hyaluronan, sulfobetaine, poloxamine, boric acid, sodium borate, edetate disodium, and sodium chloride.

##### **What dosage forms it comes in:**

Biotrue™ multi-purpose solution is available in sterile 60 mL, 120 mL, 240 mL, 300 mL and 480 mL plastic bottles.

#### WARNINGS AND PRECAUTIONS

##### **IMPROPER USE OF CONTACT LENSES AND LENS CARE PRODUCTS COULD RESULT IN CORNEAL INFECTION AND/OR ULCER AND LEAD TO LOSS OF VISION.**

It is essential that you follow your eye care professional's directions and all labelling instructions for proper use of lenses and lens care products, including the lens case.

Eye problems, including corneal ulcers, can develop rapidly and lead to loss of vision. Daily wear lenses are not indicated for overnight wear and should not be worn while sleeping. Clinical studies have shown the risk of serious adverse reactions is increased when these lenses are worn overnight. Extended wear lenses should be regularly removed for cleaning and disinfection or for disposal and replacement on the schedule prescribed by your eye care professional. Clinical studies have shown that there is an increased incidence of serious adverse reactions in extended wear contact lens users as compared to daily wear contact lens users. Studies have also shown that the risk of serious adverse reactions increases the longer extended wear lenses are worn before removal for cleaning and disinfection or for disposal and replacement. Studies have also shown that smokers have a higher incidence of adverse reactions. If you experience eye discomfort, excessive tearing, vision changes, redness of the eye, immediately remove your lenses and promptly contact your eye care professional. It is recommended that contact lens wearers see their eye care professional twice each year, or if directed, more frequently.

You should follow the complete recommended lens rubbing and rinsing times in the product labeling to adequately disinfect your lenses and reduce the risk of contact lens contamination. Reduced rubbing or rinsing time may not adequately clean your lenses.

**Failure to discard solution from lens case after each use or use of water to care for your lenses may lead to contamination resulting in eye injury and potential loss of vision. See accompanying instructions for additional important safety information.**

**Important Safety Information:**

- Visit your eye care professional regularly.
- To avoid contamination, do not touch tip of container to any surface. Replace cap after using.
- Do not use with heat (thermal) disinfection.
- Do not instill Biotrue™ directly in the eye.

**Precautions:**

- Store solution at room temperature.
- Use before the expiration date marked on the carton and bottle.
- Discard any remaining solution 90 days after opening.

**INTERACTIONS WITH THIS PRODUCT**

No interactions are known. Biotrue™ multi-purpose solution is for use with soft contact lenses, including silicone hydrogel lenses.

Not for use with heat (thermal) disinfection.

**PROPER USE OF THIS PRODUCT**

To condition, clean, remove protein and disinfect lenses daily, complete these simple steps.

**STEP 1:** Place at least 3 drops of Biotrue™ multi-purpose solution on each side of lens surface and gently rub for 20 seconds.

**STEP 2:** Thoroughly rinse each side of the lens for 5 seconds with Biotrue™ multi-purpose solution.

**STEP 3:** Place cleaned contact lenses in the lens case and fill with fresh Biotrue™ multi-purpose solution. Soak at least 4 hours. Remember to always use fresh solution – discard solution from lens case after each use.

Your lenses are now ready to wear. If any debris remains on contact lenses, rinse with Biotrue™ multi-purpose solution prior to insertion.

Always follow your eye care professional's instructions. Based upon your individual tear chemistry and lens-wearing schedule, your eye care professional may recommend additional products or procedures.

If not wearing contact lenses immediately, store them in a closed lens case. Do not store your lenses in simple saline, tap or distilled water, saliva or any non-sterile solution. These solutions will not disinfect. Lenses may be stored in the unopened case until ready to wear, up to a maximum of 30 days. If you store your lenses for longer periods of time, they must be cleaned and disinfected with fresh Biotrue™ multi-purpose solution prior to lens insertion. Replace your lens case frequently, depending upon your hygiene habits.

**Good lens care hygiene:**

- Always wash and rinse your hands before you handle your lenses.
- Clean, rinse and disinfect your lenses each time you remove them.
- Always handle the same lens, the right or the left, first in order to avoid mix-ups.
- After use, always empty and rinse the lens case with fresh Biotrue™ multi-purpose solution, and allow to air dry. In order to permit excess solution to drain, you can flip over your lens case while air drying.
- Always discard solution from lens case after each use.
- Keep the bottle tightly closed when not in use.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

The following problems may occur: 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 discomfort or problem stops, then look closely at the lens.



- If the lens is in any way damaged, do not put the lens back on your eye. Place the lens in the storage case and contact your eye care professional.
- If the lens has dirt, an eyelash, or other foreign body on it, or the problem stops and the lens appears to be undamaged, thoroughly clean, rinse and disinfect the lens, then reinsert it.
- 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 (small blood vessels growing into the cornea) or iritis (internal inflammation of the colored part of the eye (iris)) may be present. Seek immediate professional identification of the problem and prompt treatment to avoid serious eye damage.

*This is not a complete list of side effects. For any unexpected effects while using Biotrue™ multi-purpose solution, contact your eye care professional or pharmacist.*

## HOW TO STORE IT

Store solution at room temperature. Keep out of the reach of children.

### **REPORTING SUSPECTED SIDE EFFECTS**

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect)
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program  
Health Canada  
Postal Locator 0701D  
Ottawa, Ontario  
K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at [www.healthcanada.gc.ca/medeffect](http://www.healthcanada.gc.ca/medeffect).

*NOTE: Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.*

## MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found at <http://www.bausch.ca> or by contacting the sponsor, Bausch & Lomb, Inc. at: 1-800-459-5000

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