

Safety and comfort evaluation of a new formulation of Visine[®] lubricant eye drops containing HydroBlend[™] and GentlePur[™]

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Purpose: To evaluate the clinical safety and comfort of a new benzalkonium chloride-free Visine[®] lubricant eye drop formulation (Hydroblend[™] and GentlePur[™]) in healthy and dry eye subjects.

Methods: This was a single-site, open-label clinical study comprised of 22 healthy and 22 dry eye subjects. Subjects were instructed to instill 1–2 drops of the test product four times a day for 2 weeks and were examined at visit 1 (day 0), visit 2 (day 7), and visit 3 (day 14). Assessments at each visit included postdosing product usage comfort scores, predosing fluorescein corneal staining score, predosing visual acuity, and pre- and postdosing ocular structure change using slit-lamp biomicroscopy. Adverse events were monitored throughout the course of the study.

Results: Throughout the 14 days of the trial period, subjects from both healthy and dry eye groups rated the eye drops as “very comfortable”. For dry eye group, the mean product usage comfort scores for the first 3 minutes postdosing ranged from 8.5 to 8.8 at visit 1 and 9.2 to 9.6 at visit 3 on a 0–10 point scale, with 0 being very uncomfortable and 10 being very comfortable. The mean corneal staining scores over five corneal regions changed from 0.65 at visit 1 to 0.39 at visit 3 for dry eye group. The individual region corneal staining scores were also decreased from visits 1 to 3 for dry eye group. All subjects maintained pretreatment means visual acuity at visits 2 and 3. Biomicroscopic examination indicated no structural changes at all visits. There were no significant adverse events reported during the course of the study.

Conclusion: The study confirms that GentlePur[™] is an appropriate choice as a preservative for ocular application. The new formulation was safe and comfortable when used four times a day in healthy and dry eye subjects.

Keywords: lubricant eye drop, preservative, safety, polyquaternium-42, GentlePur[™], benzalkonium chloride (BAK), Hydroblend[™]

Introduction

According to the 2007 Report of the International Dry Eye Workshop,¹ dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort,^{2–4} visual disturbance,^{5–7} and tear film instability^{8–10} with potential damage to the ocular surface.¹¹ It has been estimated that approximately 5 million Americans 50 years and older have moderate-to-severe forms of dry eye, with millions more affected by less severe forms of the disease.^{12,13} While dry eye has traditionally affected older patients, the population of dry eye sufferers has been trending toward a younger age group in recent years. This is likely due to factors such as increases in laser vision correction procedures, chronic ocular allergies, and the growing numbers of persons who perform visual tasks over long period of time.¹⁴

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The varying severity and complexity of dry eye make it a challenging disease to treat. Without proper treatment, dry eye disease can adversely affect the quality of life,¹⁵ visual function,¹⁶ contact lens tolerance,¹⁷ and refractive surgery outcomes.¹⁸ Lubricant eye drop (also known as artificial tear) remain as the first line of treatment for dry eye and are commonly used to supplement for deficient natural tears.¹⁹ Like most multidose topical formulations for ocular use, these tear substitutes contain preservatives to inhibit microbial contamination. While preservatives are not required in unit dose vials, these nonpreserved preparations are more costly for the patients to purchase and less convenient to use than ocular lubricants in multidose packaging. Among common ophthalmic preservatives, benzalkonium chloride (BAK, BZK, or BAC) was the first ophthalmic preservative and has been in use for over 60 years.²⁰ BAK is a quaternary ammonium surfactant preservative and is currently used in over 70% of ophthalmic products on the market.²¹ While the preservative efficacy (PE) of BAK is well established, it has also come under scrutiny over the years for its potential to disrupt the precorneal tear film and damage the epithelial surface of the cornea, especially for dry eye patients who use the product frequently.^{22–27} To avoid the potential risks associated with BAK use in dry eye patients, many commercially available tear substitute products now offer preservative-free or BAK-free solutions.

A systematic development program was initiated to identify, characterize, and validate a novel, safe, effective, and gentle preservative as an alternative to BAK. The preservative was required to meet three fundamental criteria: 1) potency of PE; 2) potential lack of ophthalmic or systemic toxicity based on available literature data; 3) potential lack of reactivity to other commonly used ophthalmic ingredients.

After a thorough literature search, a list of preservatives that may have potential for ophthalmic use was generated. A preservative effectiveness test on all preservatives using a lubricant eye drop formula without BAK was carried out, and the products with adequate PE were selected. Subsequently, a series of *in vitro* studies including transepithelial permeability, fluorescein leakage, and the neutral red uptake cytotoxicity procedure were conducted using BAK as the negative control. Results from the neutral red uptake procedure were most discerning regarding the cytotoxicity of the preservatives. On the basis of all the *in vitro* test results, polyquaterium-42 (GentlePur™) demonstrated superior preservative effectiveness and much less irritability than BAK.

GentlePur™ is a quaternary ammonium cationic surfactant polymer that contains straight polyethylene chain segments. In comparison, BAK is a quaternary ammonium cationic

surfactant monomer that contains benzyl rings segments. Although both are highly effective antimicrobial agents, GentlePur™ has extremely low ocular irritancy and has been used as a preservative in contact lens solutions and lubricant eye drops.^{28,29}

The purpose of this study was to evaluate the comfort and safety of a new formulation of Visine® (Johnson & Johnson, New Brunswick, NJ, USA) lubricant eye drops containing GentlePur™ and 0.2% glycerin, 0.36% hypromellose, and 1% polyethylene glycol 400 “Hydroblend™” in healthy and dry eye subjects.

Methods

Study population

This study was conducted in compliance with the ethical principles of Good Clinical Practices, the Declaration of Helsinki, the International Conference on Harmonization guidelines, and all applicable local and federal requirements relevant to the use of investigational drugs. The study employed a single-site, open label, investigator-masked protocol. The two study groups enrolled 22 subjects each; one group of subjects was a healthy control group, the other group of subjects had a confirmed diagnosis of dry eye. Inclusion criteria for both groups were as follows: subjects needed to be at least 18 years old, follow all study directions, and attend all required visits, and provide written informed consent for study participation. All subjects had corrected visual acuity of logMar +0.5 (ETDRS, Early Treatment Diabetic Retinopathy Study) or better in each eye and good overall ocular health (with the exception of the dry diagnosis). Subjects were excluded if they had used contact lenses within 1 week of the study or were planning to wear contacts within the anticipated study timeframe; had any active ocular inflammation or allergy; had used any topical ophthalmic agents within 7 days of the study; had ever undergone laser-assisted *in situ* keratomileusis, surgery for neurotrophic keratitis or corneal transplant; had any ocular surgery within 6 months; or were currently using any systemic medication known to cause ocular dryness. Subjects with known sensitivities to any study components or those with any medical condition that could affect study parameters were also excluded, as were women of childbearing age who were pregnant or unwilling to use approved birth control for the duration of the study. Subjects who had participated in any other clinical trial in the previous 30 days were also ineligible. To qualify for the dry eye group, subjects were required to have a history of lubricant eye drop use in the previous 12 months, and fluorescein corneal staining score ≥ 1 (National Eye Institute [NEI] scale) in any of the five regions and a total score < 7 in one eye; subjects who did

Table 1 Safety assessment schedule

	Product usage eye comfort score	Fluorescein corneal staining score	Visual acuity	Ocular structure/slit-lamp biomicroscope
Visit 1 (day 0)	Immediate, 1, 2, and 3 minutes postdosing	Predosing	Predosing	Predosing and 15 minutes postdosing
Visit 2 (day 7)	Not measured	Predosing	Predosing	Predosing and 15 minutes postdosing
Visit 3 (day 14)	Immediate, 1, 2, and 3 minutes postdosing	Predosing	Predosing	Predosing and 15 minutes postdosing

not meet both of these criteria, or subjects with a history of lubricant eye drop use ≥ 6 times per day, were excluded from both control and dry eye groups.

Test product

The test product is a prototype lubricant eye drop formulation. It combines Hydroblend™ (0.2% glycerin, 0.36% hypromellose, and 1% polyethylene glycol 400) and the preservative GentlePur™ (polyquaternium-42).

Study protocol

The study duration was 2 weeks. Each subject attended three study visits: visit 1 (day 0, baseline), visit 2 (day 7 \pm 1), and visit 3 (day 14 \pm 1). Following baseline assessment on day 0, all subjects were provided with test lubricant eye drop and instructed to instill the drops into each eye (1–2 drops) four times a day for 14 days. Assessments conducted at each visit included visual acuity, ocular structure change using slit-lamp biomicroscopy, and fluorescein corneal staining (inferior, superior, central, temporal, nasal) based on the NEI scale of 0–3^{30,31} (0= normal and 3= severe). Product usage comfort assessments were conducted at visits 1 and 3 for each eye immediately and at 1, 2, and 3 minutes postdosing using a scale ranging from 0 to 10, with 0 being very uncomfortable and 10 being very comfortable. The assessment schedule is summarized in Table 1. Additionally, adverse events were monitored and recorded throughout the entire course of the study.

Statistical analysis

Forty-four subjects, 22 healthy and 22 with dry eye, were enrolled in the study. One dry eye subject was discontinued after visit 1 due to noncompliance (unable to attend visit 2). Sex was summarized by numbers and percentages, and age was summarized by means and standard deviations. Scores for each eye were obtained for visual acuity, product usage comfort, and corneal staining (inferior, superior, central, temporal, nasal, and average over the five regions). These were averaged over the two eyes to give corresponding subject-level scores, and the subject-level scores were averaged over all subjects to give mean group scores.

Results

Study population

A total of 56 subjects were screened to identify 22 subjects for each study group. After the study began, one subject from the dry eye group was discontinued due to noncompliance. A summary of demographics is presented in Table 2. Overall, the dry eye group was somewhat older and had a larger number of women, as expected from the prevalence of the disease in the general population.

Product usage eye comfort score

At the first (visit 1) and last (visit 3) study visits, subjects were asked to provide assessments of drop comfort for each eye immediately after instillation and at 1, 2, and 3 minutes following instillation. The assessments used a 0–10 point scale, where 0 is very uncomfortable and 10 is very comfortable. Mean values of four time points at each visit, shown in Table 3 and Figure 1A and B, are all 8.50 or higher for all time points, visits, and subject groups.

Corneal staining score

Fluorescein staining of the corneal surface from inferior, superior, central, temporal, nasal region, and an average over the five regions based on the NEI scale of 0–3 (0= normal and 3= severe) was assessed and the results are included in Table 4.

For the dry eye group, the five-region corneal staining scores improved from visits 1 to 3. The average staining scores over the five regions of the cornea were 0.65 at visit 1, 0.75 at visit 2, and 0.39 at visit 3. A decrease in corneal fluorescein staining from baseline (visit 1) to visit 3 for dry eye group is presented in Figure 2.

Table 2 Subject demographics

	Dry eye (N=22)	Healthy (N=22)
Sex	N (%)	N (%)
Female	18 (82%)	13 (59%)
Male	4 (18%)	9 (41%)
Age	Mean (\pm standard deviation)	Mean (\pm standard deviation)
Female	54 (\pm 12)	38 (\pm 11)
Male	45 (\pm 16)	44 (\pm 14)

Table 3 Subject reported product usage comfort scores after product usage

	Dry eye group		Healthy eye group	
	Visit 1 (N=22)	Visit 3 (N=21)	Visit 1 (N=22)	Visit 3 (N=22)
Immediate	8.55±1.22	9.24±1.34	9.82±0.39	9.36±1.18
1 minute	8.68±1.09	9.62±0.80	9.77±0.53	9.64±0.79
2 minutes	8.50±1.26	9.57±0.87	9.73±0.63	9.86±0.35
3 minutes	8.82±1.00	9.52±0.92	9.64±0.95	9.90±0.29
Mean ± standard deviation	8.64±0.90	9.49±0.80	9.74±0.59	9.69±0.54

Note: The values are given as mean ± standard deviation.

For the healthy group, the corneal staining scores at baseline were very low (0.15) and they showed very little changes from baseline at visits 2 and 3.

Visual acuity

Averaging over both eyes, pretreatment (baseline) visual acuity means on the logMAR scale were 0 and -0.02 for the dry eye subjects and healthy subjects, respectively. For both groups, visual acuity means were maintained at visit 2 and improved by 0.03 at visit 3.

Ocular structure using slit-lamp biomicroscopy

Slit-lamp biomicroscopy was conducted on four ocular structures (lid, lens, conjunctiva, and cornea) predose and postdose at all three visits for a total of six time points. For all structures, the five posttreatment findings showed no change from visit 1 pretreatment findings.

Adverse events

In addition to the acuity and slit-lamp examinations, a tabulation of all reported adverse events was used in the overall safety assessment. Reported adverse events were mild and did not require action to mitigate the effects observed. Two dry eye subjects had a total of four adverse events from the entire study

population. Two adverse events (filmly vision upon instillation and blurred vision after instillation) were related to the study medication. The other two adverse events (ocular redness and increased tears) were possibly related to the study medication. All adverse events were assessed as mild and nonserious. There were no discontinuations due to the study medication.

Discussion

In order to determine the potential for ocular irritation by GentlePur™ and provide data to support its use in humans, a rabbit study was conducted. In this study, ten rabbits were dosed with lubricant eye drops preserved with GentlePur™ six times daily for 30 consecutive days. This study established that topical administration of the preservative was nontoxic and nonirritating in the rabbit eye test system.

In the current study, GentlePur™ preserved lubricant eye drops were tested for eye comfort and safety in both a healthy control group and in subjects with mild dry eye disease. At the beginning and the end of 2 weeks of treatment, all subjects found the product to be comfortable to use, with product usage eye comfort means of 8.5 or higher on a scale of 0–10, where 0 is very uncomfortable and 10 is very comfortable, indicating a high tolerance of the test product for both dry eye and healthy eye subjects. From visits 1 to 3, the eye comfort score at each time point (immediately, 1, 2,

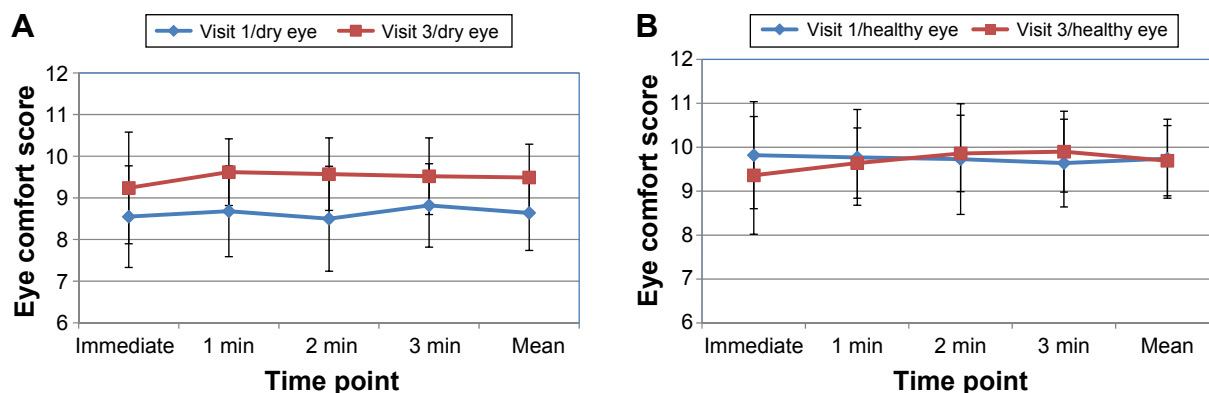


Figure 1 Mean of subjects' reported product usage eye comfort score for dry eye (A) and healthy eye (B) groups.

Table 4 Mean corneal staining for dry eye and healthy eye groups from each region and average across five regions

	Dry eye group			Healthy eye group		
	Visit 1	Visit 2	Visit 3	Visit 1	Visit 2	Visit 3
Inferior	1.02±0.11	1.35±0.1	0.83±0.11	0.27±0.11	0.34±0.11	0.39±0.10
Central	0.20±0.07	0.10±0.07	0.17±0.07	0.07±0.03	0.05±0.05	0.05±0.05
Superior	0.55±0.11	0.81±0.07	0.05±0.05	0.14±0.05	0.23±0.08	0.02±0.02
Temporal	0.48±0.10	0.62±0.09	0.29±0.09	0.07±0.04	0.07±0.03	0.05±0.03
Nasal	1.00±0.13	0.88±0.06	0.62±0.10	0.18±0.07	0.11±0.05	0.02±0.02
Average across five regions	0.65±0.07	0.75±0.04	0.39±0.06	0.15±0.04	0.16±0.04	0.10±0.03

Note: The values are given as mean ± standard error.

and 3 minutes after dosing) and mean eye comfort score over four time points increased numerically for dry eye subjects and maintained nearly no change for healthy eye subjects (Table 3 and Figure 1A and B).

Corneal fluorescein staining has been recognized as a reliable clinical measurement for ocular surface condition and is correlated with the severity of dry eye. Per study protocol inclusion criteria, dry eye subjects were selected with corneal staining score of ≥ 1 in any of the five regions on the NEI scale in at least one eye. Therefore, it is expected that dry eye group had higher baseline corneal fluorescein staining score than that of healthy subjects in all five corneal regions. Although the corneal staining score increased from visits 1 to 2, it decreased from visits 1 to 3 for all five regions in dry eye group, indicating an overall improvement from the new lubricant eye drop treatment for dry eye patients. For the healthy eye group, the mean baseline corneal staining score was very low (0.15) and remained very low (0.10) at the end of the 2-week treatment, indicating no increase of eye dryness for healthy eye subjects (Table 4 and Figure 2).

Over the trial period there was also no evidence of deteriorating outcomes in visual acuity following treatment. In fact, similar to corneal staining, there was a tendency for slight improvement from visits 1 to 3. Product usage comfort increased slightly with use for dry eye subjects and was fairly consistent for healthy subjects.

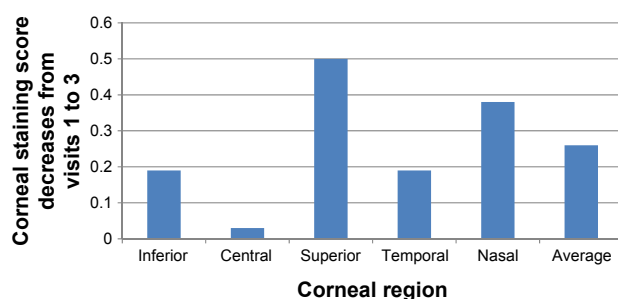


Figure 2 Mean corneal staining decrease (improvement) from visits 1 to 3 in dry eye group.

Slit-lamp biomicroscopic examination on four ocular regions did not find any structural change after 2 weeks of treatment from the baseline. While there were four adverse events reported in this study, all were considered to be mild and nonserious, as there were no discontinuations due to the study medication, and all four events resolved by the end of the study date or shortly thereafter.

Conclusion

The prototype lubricant eye drop formulation from the makers of Visine® combines a gentle and effective preservative GentlePur™ with unique Hydroblend™ technology to provide a new lubricant eye drop option for dry eye sufferers and can be used as often as needed as directed by label instructions.

Acknowledgment

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Disclosure

The authors report no conflicts of interest in this work.

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