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REVIEW

Systane® lubricant eye drops in the management of ocular dryness

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Abstract: The understanding of dry eye disease has advanced recently through increasing recognition that the etiology of the condition involves both tear evaporation and insufficient tear production, and that tear film instability and inflammation play roles in the various stages of the disease. Of significance, it has been recognized that lipid layer thickness correlates with tear film stability. The management of dry eye involves various strategies and therapeutic approaches that address one or more etiopathological components of the disease. The purpose of this review is to outline the characteristics and clinical utility of the Systane® ocular lubricants that contain hydroxypropyl-guar and one or both of the demulcents, ie, polyethylene glycol 400 and propylene glycol. Clinically, these products are safe and are indicated for the temporary relief of burning and irritation due to dryness of the eye. In particular, this review describes the formulations, mechanisms of action, and clinical utility of the newest additions to this topical ocular lubricant family, Systane Ultra® and Systane Balance®. Both of these ocular products are formulated with an intelligent delivery system and both provide symptomatic relief to patients with dry eye. However, Systane Balance is a novel formulation that contains both polymer and lipid components designed to protect the ocular surface and replenish tear film lipids simultaneously, a factor that is of particular relevance to patients who have dry eye associated with meibomian gland dysfunction.

Keywords: Systane Ultra, Systane Balance, dry eye, hydroxypropyl-guar, meibomian gland dysfunction, dimyristoylphosphatidylglycerol

Introduction

Dry eye disease is a multifactorial ocular condition that results from an inadequate quantity of tear film and/or a disturbance of tear film stability. In 2007, the International Dry Eye Workshop subcommittee for definition and classification expanded the definition of dry eye disease, beyond tear deficiency and evaporation, to include tear film degradation and potential damage to the ocular surface.[1] Additionally, this subcommittee recognized the contributions to the disease process of hyperosmolarity of the tear film and inflammation of the ocular surface.[1]

The moisture of the eye is maintained by the tear film, which consists of an aqueous layer (secreted by the lacrimal glands), a mucus layer (produced by conjunctival goblet cells and by corneal and conjunctival epithelial cells), and a lipid layer (secreted primarily by the meibomian glands).[2–4] Any alterations in the volume, composition, distribution, and/or clearance of the tear film can lead to dry eye disease. Based on etiology, dry eye can be categorized as aqueous tear-deficient or evaporative. Aqueous tear-deficient dry eye may be a result of Sjögren's syndrome (primary disease or

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secondary to other autoimmune diseases, such as rheumatoid arthritis or systemic lupus erythematosus) or non-Sjögren factors, including lacrimal gland insufficiency, lacrimal duct obstruction, or reflex hyposecretion. Evaporative dry eye may also be caused by several factors including, but not limited to, meibomian gland dysfunction, eyelid aperture disorders or lid/globe incongruity, blink disorders, and ocular surface disorders.[2,5]

The global prevalence of dry eye, estimated from large studies, ranges widely from approximately 5% to 35%.[6] Patients who suffer from dry eye have varying levels of symptoms, such as ocular dryness, burning, photophobia, foreign body sensation, grittiness, and redness, and may or may not have clinically meaningful signs, such as rapid tear film breakup time, increased osmolarity, and increased ocular surface staining.[7,8] Individuals with dry eye also commonly experience disturbances in visual function, which have considerable negative impacts on their ability to carry out daily tasks (eg, driving and participating in sports and other leisure activities, such as reading and cooking).[9] Since these limitations also have negative effects on overall quality of life, therapies that provide relief from the symptoms of dry eye are also likely to provide beneficial effects related to daily functioning and quality of life.[10]

The most common cause of evaporative dry eye disease is meibomian gland dysfunction, a condition associated with lipid insufficiency and/or poor lipid spreading, which results in a failure to form a continuous and homogeneous tear film. Ultimately, this failure leads to increased aqueous tear evaporation and decreased tear film stability.[11,12] Although the evaporation rate of the tear film is determined by multiple factors, including the protein constituents of the tear film, the mucin coating of the epithelial cells, and the aqueous component of lacrimal secretions, the status of the lipid layer is critical.[11] In particular, the thickness of the lipid layer affects evaporation and a thicker tear film lipid layer is correlated with better tear film stability.[13–15] Further, a recent study showed that the thickness of the lipid layer, as measured by interferometry, is well correlated with dry eye symptoms in routine clinical practice.[16] Thus, an important feature of any dry eye therapy intended to provide relief to patients with meibomian gland dysfunction is the ability to mimic the lipid layer of the tears.

Management of dry eye disease

Over the past two decades, there has been substantial progress in the understanding of the etiological and pathophysiological aspects of dry eye disease. This has led to an evolution, not only in the way the disease is defined, but also in the way it is managed. Given the multifactorial nature of dry eye, management may involve various strategies and therapeutic approaches intended to minimize evaporative tear loss, stabilize the tear film, protect the ocular surface, repair ocular surface damage, increase lubrication, enhance glandular secretion, and curb inflammation.[17] In particular, the primary management goals are to restore the natural homeostasis of the ocular surface and tear film and to improve the patient's ocular comfort and quality of life.[9,18]

Current approaches to the management of this condition include the use of topical lubricants (artificial tears or biological tear substitutes), systemic antibiotics (eg, tetracycline, doxycycline, and minocycline), topical anti-inflammatory therapies (eg, corticosteroids or the immunomodulator, cyclosporin), nutritional therapies (eg, dietary intake of omega-3 fatty acids), and tear stimulants (eg, secretagogues, such as cholinergic agents). Additionally, the control of external factors associated with increased ocular dryness (eg, humidity) is a key component of managing the disease.[3]

Artificial tears

Dry eye results in disruption of the tear film and subsequent damage to epithelial cells on the ocular surface, which, in turn, may aggravate the observed signs and the symptoms of the disease experienced by the patient. While these damaged cells are being replaced, the ocular surface remains vulnerable to further injury.[19] According to the International Dry Eye Workshop report, early intervention could disrupt the core mechanism that drives dry eye[1] and thus, by extension, an artificial tear with a demonstrated ability to restore ocular surface health may help to arrest progression of the disease. Regardless of the etiology and severity of dry eye, artificial tears are the mainstay of therapy.[20] In addition to being safe and effective, the ideal topical ocular lubricant is characterized by its ability to spread efficiently, quickly, and evenly over the cornea, to minimize friction between the upper eyelid and the cornea, to cause minimal blur upon instillation, and to improve both the subjective symptoms and the objective signs of dry eye.[20]

Artificial tear formulations are typically buffered solutions that contain electrolytes, surfactants, and one or more viscosity agents or lubricants, eg, guar-based and cellulose-based derivatives, including hydroxypropyl-guar, as well as glycerin, dextran, polyvinyl alcohol, polyethylene glycol 400, and propylene glycol, and may or may not also contain a preservative. Although most artificial tear products contain

similar ingredients, they differ in the types of lubricants used and in their mechanisms of action.[4,21,22] Despite the availability of numerous marketed artificial tears, many of these products have been found to relieve the symptoms of dry eye only temporarily, rather than to heal the ocular surface or to treat the underlying cause of the disease.[4] Given the drawbacks of many currently available artificial tear formulations, and recognizing the advances in understanding of the global mechanisms underlying dry eye disease, the Systane® family of products (Alcon Laboratories Inc, Fort Worth, TX) was developed to address not only the tear film disorder, but also disruptions of the ocular surface itself.[23]

Systane family of lubricant eye drops

The Systane family of topical ocular products intended for use in patients with dry eye includes Systane lubricant eye drops, Systane preservative-free lubricant eye drops, Systane Ultra lubricant eye drops, Systane Ultra preservative-free lubricant eye drops, and, most recently, Systane Balance lubricant eye drops.[24] These products, all of which include propylene glycol, hydroxypropyl-guar, and, with the exception of Systane Balance, polyethylene glycol 400, collectively represent a new generation of artificial tear preparations. They are theorized to work through a unique biphasic mechanism of action in which the product first binds to damaged hydrophobic areas of epithelial cells to add volume to the tear film, and then restructures the tear film by forming a protective gel matrix that provides long-lasting protection.[19] The high molecular weight (1000–5000 kDa) hydroxypropyl-guar molecules, along with the natural mucin layer, prolong retention of the demulcents on the ocular surface, which provides sustained lubrication to the eye and protects the ocular surface from further damage while the surface epithelial cells undergo repair and renewal.[19,25]

With the exception of the preservative-free formulations, Systane lubricant eye drops are preserved with polyquaternium-1 (Polyquad®, Alcon Laboratories, Inc). Polyquaternium-1 is a bactericidal quaternary ammonium compound that has been used as a preservative in contact lens storage solutions and lubricant eye drops. At the concentration used in Systane products (0.001%), this preservative is safe and has been shown to have no effects on the cytokinetic movement, morphology, or mitotic activity of cultured human corneal epithelial cells after a 24-hour exposure period.[26]

In recent reviews and studies, evidence has been provided to show that in vitro, under conditions that mimic the ocular surface of a patient with dry eye, Systane exhibits a superior profile in the areas of tear film breakup time, extensional viscosity, coefficient of friction, and lubrication when compared with other marketed products, including saline solution, carboxymethylcellulose-containing formulations like Refresh Tears® (Allergan Inc, Irvine, CA) and Optive™ lubricant eye drops (Allergan), and polyethylene glycol 400-containing Blink Tears® (Abbott Laboratories Inc, Abbott Park, IL), among others.[20,21,27]

In clinical studies, the daily use of Systane for 28 days or more in patients with dry eye has been consistently associated with significant decreases in conjunctival and/or corneal staining,[7,19,23,28,29] increases in tear film breakup time (invasive or noninvasive),[30–34] and improvements in patient-assessed parameters (drop comfort, ocular comfort, and dry eye symptoms).[7,19,28,29,33,34] Further, in several clinical studies comparing Systane with other marketed lubricant eye drops, Systane generally was superior to the active comparator or saline. Specifically, Systane was more effective in reducing ocular surface staining compared with Refresh Tears (0.5% carboxymethylcellulose),[19] and was more effective in extending tear film breakup time compared with Sensitive Eyes® saline solution (Bausch and Lomb, Rochester, NY),[35] Lens Plus® saline solution (Advanced Medical Optics, Santa Ana, CA),[32] Refresh Tears, and Refresh Endura® lubricant drops (carbomer 1342, castor oil, glycerin, mannitol, and polysorbate 80, Allergan).[30] Additionally, in patients with dry eye, the administration of Systane was associated with a significantly greater ($P < 0.05$) ocular protection index relative to Refresh Tears and Refresh Endura at various time points after instillation;[30] note that the ocular protection index, which is derived from the tear film breakup time and the blink interval, is often used as a surrogate measure of the level of ocular surface protection provided by the tear film.[36] Finally, the combined use of Systane with cyclosporin 0.05% for 6 months resulted in significantly greater ($P < 0.05$) reductions in corneal staining and the most common symptoms of dry eye (dryness, burning, grittiness, and foreign body sensation) when compared with the combined use of Refresh Tears and the same cyclosporin fomulation.[37] Overall, a review of the clinical efficacy and safety of Systane reveals that this formulation yields long-lasting relief of dry eye symptoms, improves the signs associated with dry eye disease, provides an enhanced environment for ocular surface protection, and is well tolerated by patients with dry eye.[21]

While the Systane family of lubricant eye drops are indicated for the temporary relief of burning and irritation due to dryness of the eye, Systane Ultra and Systane Balance deliver

extended ocular surface protection and symptom relief to patients with dry eye. Furthermore, Systane Balance was specifically designed for patients with dry eye associated with meibomian gland dysfunction. An overview of these recent additions to the Systane family follows.

Systane Ultra lubricant eye drops

Formulation and mechanism of action

Systane Ultra, like Systane, includes two demulcents (polyethylene glycol 400 and propylene glycol) and a gelling agent (hydroxypropyl-guar); the product is also buffered with borate, which results in a partially crosslinked borate/hydroxypropyl-guar gel.[23,38] However, unlike Systane, Systane Ultra includes sorbitol, which serves to optimize the viscosity of the drop through control of the aforementioned borate/hydroxypropyl-guar gel. In the bottle, the pH of Systane Ultra is 7.9 and the sorbitol/borate/hydroxypropyl-guar complexes are in a state of dynamic equilibrium. When a drop is instilled, the pressure exerted on the bottle to extract the drop reduces gel viscosity through shear thinning. Upon instillation, this physical process, along with ocular surface characteristics that dilute sorbitol and increase the density of the borate/hydroxypropyl-guar crosslinks, produces a gel of very low viscosity that is maintained between blinks.[22] The combined effect is intended to prevent blurring or haze upon instillation, reduce friction during blinking, and yield prolonged ocular comfort. Finally, the interaction of Systane Ultra with natural divalent ions in the tear film (eg, calcium, zinc, and magnesium) fortifies the borate/hydroxypropyl-guar crosslinks and prolongs retention of the demulcents on the ocular surface.[4,22,39]

Clinical studies

The efficacy, tolerability, and/or safety of Systane Ultra have recently been evaluated in two clinical studies. The first of these was a prospective, double-masked, randomized, multicenter, parallel group study designed to evaluate the safety and efficacy of Systane Ultra relative to Optive, which contains 0.5% carboxymethylcellulose and 0.9% glycerin.[40] The second of these was a prospective, double-masked, randomized, single-center, parallel group study designed to evaluate the safety of Systane Ultra relative to Sensitive Eyes (isotonic saline solution).[39]

The safety and efficacy study included 113 patients, 18 years of age and older, who had dry eye. After a 2-week run-in period during which patients administered aqueous saline eye drops four times daily in each eye, patients were randomized (1:1) to receive either Systane Ultra or Optive; the masked products were administered four times daily in each eye for 6 weeks. Efficacy was evaluated by comparing corneal and conjunctival staining scores, tear film breakup times, assessments of ocular symptoms (dryness, gritty/sandy sensation, burning, redness, crusting on eyelashes, and eyes sticking shut in the morning), Ocular Surface Disease Index scores, and responses to the Dry Eye Treatment Satisfaction and Visual Function-14 questionnaires; safety was assessed through a review of ocular examination findings and reported adverse events.

In the most critical sign-based indicators of long-term dry eye relief evaluated in this study (ie, reductions in corneal and conjunctival staining), Systane Ultra was found to be superior to Optive. Specifically, compared with patients in the Optive group, patients in the Systane Ultra group had significantly lower mean corneal staining scores at day 14 ($P = 0.0009$) and day 42 ($P = 0.0106$), and had significantly lower mean conjunctival staining scores at day 28 ($P = 0.0475$) and day 42 ($P = 0.0009$). At the end of the study, patients in both study product groups reported high levels of satisfaction with their therapy and had significantly lower Ocular Surface Disease Index scores relative to baseline ($P \leq 0.0013$ for each pairwise comparison within each study product group). Further, patients in both study product groups reported significant decreases in the ocular symptoms (dryness, sandy/gritty feeling, and burning) associated with dry eye ($P \leq 0.0021$ for all comparisons within study product groups between day 42 and baseline). Finally, no patient experienced changes in slit lamp findings or visual acuity assessments, and, based on a review of reported adverse events, no safety signals were identified.[40]

The separately conducted safety study included 45 patients who had dry eye and were successful contact lens wearers. In this study, patients were randomized (1:1) to receive either Systane Ultra or Sensitive Eyes. Regardless of study product assignment, patients instilled the masked lubricant into each eye 15 minutes prior to lens insertion (1–2 drops per eye), during the period of lens wear (at least one additional drop per eye), and immediately following lens removal (1–2 drops per eye). Safety was evaluated through a review of biomicroscopy results, visual acuity assessments, and corneal staining scores. In this study, no adverse events were reported and the use of Systane Ultra in successful contact lens wearers was not associated with any significant changes in corneal staining, biomicroscopy findings, or distance visual acuity.[39] Overall, the results of these studies variously show that Systane Ultra is effective in reducing the signs and symptoms associated with dry eye, and is safe

when used by patients with dry eye. Of particular importance to safety, the lubricating eye drops are well tolerated among patients who wear contact lenses.

Systane Balance lubricant eye drops

Formulation and mechanism of action

While most artificial tears or topical ocular drops that replenish the aqueous layer are designed to promote lubrication, they do not address the issue of lipid deficiency that is commonly associated with dry eye. Because this issue is critical for patients with evaporative dry eye in general, and patients with meibomian gland dysfunction in particular, Systane Balance, an hydroxypropyl-guar gellable lubricant eye drop containing micro-emulsions of oils (LipiTech™ system), was specifically formulated to minimize the evaporative loss of tears from the ocular surface.

Systane Balance contains propylene glycol, hydroxypropyl-guar, borate, and sorbitol, and additionally includes both a polar phospholipid surfactant (dimyristoylphosphatidylglycerol) and mineral oil.[41] These latter two components were included to mimic the lipid layer of the tears. Specifically, polar lipids in the tear film are proposed to act as surfactants that help spread nonpolar lipids over the aqueous components of the tear film, thus providing a barrier between the two layers and a supportive structure for the nonpolar phase. It is the combination of this barrier and structure that creates a seal, which serves to decrease tear evaporation.[17]

A number of physicochemical studies were conducted with Systane Balance, including particle size measurements from light scattering, droplet charge estimations from electrophoresis, viscosity and shear stress profiles from rheology, and coefficient of friction assessments from a specially designed tribometer. Additionally, interfacial and surface chemistry studies were performed using contact angle measurements to estimate surface tension and spreading pressure. Finally, light microscopy was used to document spreading and mixing properties of the emulsion, while electron micrographs were used to show the retention and release of oil droplets by hydroxypropyl-guar. Collectively, data from these studies show that Systane Balance is a stable emulsion, with small droplet size, and low viscosity, which is adhesive on the ocular surface and can stabilize and structure interfaces.[42]

As a result of its low viscosity and neutral pH, Systane Balance is predicted to be comfortable when instilled, with minimal blurring. Prior to instillation (at pH 7), the drop has low viscosity, which allows for efficient mixing and spreading over the ocular surface. After instillation (at the higher pH of the ocular surface), the structured viscoelastic hydroxypropyl-guar polymer network forms, provides transient adherence to the ocular surface, and delivers the oil micelles over time. Specifically, blinking, dilution, and thermodynamic forces lead to the release of the oil from the polymer onto the ocular surface, forming part of the protective lipid layer of the tear film.[46] Thus, in addition to its lubricant and surface-protective effects, Systane Balance can physically restore the tear film lipid layer.

Clinical studies

The efficacy and tolerability of Systane Balance was assessed variously in three clinical studies. The first was a randomized, double-masked, single-center, contralateral eye study designed to measure lipid layer thickness in dry eye patients who used Systane Balance compared with patients who used Soothe® XP eye drops (light mineral oil 1%, mineral oil 4.5%, octoxynol-40, and polysorbate-80, Bausch and Lomb).[43] The second was a randomized, double-masked, single-center, two-period crossover study designed to evaluate tear film breakup time, drop haze, ocular comfort, and drop acceptability in Systane Balance relative to Soothe XP.[43] Finally, the third was an open-label, single-center study designed to compare the efficacy of Systane Balance with that of habitual therapy in patients diagnosed with meibomian gland dysfunction.[44]

The first of the reported studies included 40 patients who had a baseline lipid layer thickness measuring less than 75 nm in both eyes, with less than 15 nm in variation over the course of a 10 minute observation period. In this contralateral eye study, one drop of Systane Balance was instilled in one eye of each patient and Soothe XP was instilled in the opposing eye; the eye that received each individual product was randomized. The lipid layer thickness was measured at baseline and at minutes 1, 5, 15, 60, and 120 following instillation using a custom-designed lipid layer interferometer. While both of the products evaluated in this study contain lipid components, only Systane Balance contains an active demulcent, along with emulsifiers designed to form colloidally stable oil droplets.[41] In this study, the instillation of Systane Balance resulted in a significantly greater thickening of the lipid layer relative to Soothe XP at all time points beginning at 5 minutes and continuing through 120 minutes postinstillation ($P \leq 0.0015$ for each pairwise comparison at every time point).[43] Thus, the study showed that, when compared with Soothe XP, instillation of Systane Balance produces a relatively rapid and substantially greater thickening of the tear film lipid layer.

The second of the reported studies included 38 patients with dry eye associated with meibomian gland dysfunction and a tear film breakup time of five seconds or less. In this study, all patients instilled a masked study product (Systane Balance or Soothe XP) into both eyes and were evaluated during period 1; the patients subsequently instilled the alternate masked study product into both eyes and were reevaluated during period 2. The assignment of study product to each patient was randomized by period. Following study product instillation in each period, a haze/blur profile was created at 3 minutes, with determinations made at 30-second intervals, tear film breakup time was evaluated at minutes 15, 30, 60, and 120, and comfort and drop acceptability were assessed using a standard questionnaire. Overall, compared with Soothe XP, instillation of Systane Balance yielded significantly less haze up to 1 minute after instillation ($P \leq 0.0044$ for each time point comparison), resulted in significantly more favorable drop comfort scores after instillation ($P = 0.041$), and produced significantly longer tear film breakup times at 120 minutes after instillation ($P < 0.0001$). While drop acceptability scores were better with Systane Balance than with Soothe XP, the differences did not reach statistical significance.[43]

The third of the reported studies included 49 patients who were previously diagnosed with meibomian gland dysfunction (defined by symptoms, as well as evidence of aberrant meibum and meibomian gland dropout). During the baseline visit, all patients reported detailed information regarding their habitual dry eye therapy uses. Following the baseline visit, and continuing for 28 days, all patients were instructed to use Systane Balance in place of their habitual therapies. The study endpoints included results from patient-reported symptom relief questionnaires, tear film breakup times, corneal staining scores, assessments of quality for the expressed meibum, and reports of drop usage as tracked with an automated device (Medication Event Monitoring System). Each of the study endpoints was compared with the corresponding baseline measurement (ie, the assessments performed before instillation of Systane Balance that were the result of habitual therapy use).

The results from the patient questionnaires showed that 86% of the patients thought Systane Balance provided fast symptomatic relief, 79% were satisfied with the comfort of the Systane Balance drop, and 77% reported overall satisfaction with Systane Balance. After using the study product for 28 days, relative to habitual therapy, the patients had a mean improvement in tear film breakup time of 33% and a mean reduction in corneal staining of 26%; both results were significant ($P = 0.032$ and $P < 0.001$, respectively). Additionally, a mild improvement in meibomian gland expression of 17% was observed and a moderate decrease in drop usage of 24% was also reported; again, both results were significant ($P = 0.005$ and $P < 0.001$, respectively). Thus, Systane Balance was shown to be more effective in reducing the signs and symptoms of meibomian gland dysfunction than the patients' habitual ocular therapies.[44]

Overall, these clinical studies demonstrate that topical ocular instillation of Systane Balance in patients with dry eye disease secondary to meibomian gland dysfunction is associated with substantial improvements in tear film lipid layer thickness and tear film stability up to 2 hours after instillation. Additionally, Systane Balance increases meibomian gland function and induces less haze (blur) upon instillation than a lipid-containing competitor product; the blur profile for Systane Balance is similar to that of an aqueous-based competitor product. Finally, patients perceive Systane Balance to be fast-acting, comfortable, and satisfactory; its use is associated with decreased drop dependency.

Conclusion

Current approaches to the management of dry eye disease reflect the multifactorial nature of this condition. Therapeutic strategies are designed to restore the natural tear film, protect the ocular surface, and improve the patient's ocular comfort and quality of life. Artificial tears remain the mainstay of dry eye therapy. Although there are several marketed artificial tears available, many of these products have been found to relieve the symptoms of dry eye only temporarily, do not protect the ocular surface, and are not intended to address underlying causes of dry eye, particularly tear film lipid deficiencies. The Systane family of hydroxypropyl-guar-containing gellable lubricant eye drops are formulated with an intelligent delivery system designed to provide symptomatic relief to patients with dry eye. The latest additions to the Systane family include Systane Ultra and Systane Balance. With the inclusion of sorbitol in its formulation, Systane Ultra causes minimal blurring or haze upon instillation and provides prolonged ocular comfort and relief of dry eye symptoms. Systane Ultra has been formulated to provide optimal ocular surface protection and lubrication. Systane Balance contains a unique lipid emulsion, which simultaneously protects the ocular surface and replenishes tear film lipids, a factor that is of particular relevance to patients with dry eye associated with meibomian gland dysfunction.

Systane lubricant eye drops act in a complex manner to target multiple pathologies linked to dry eye disease. They offer extended relief of dry eye symptoms and provide an enhanced environment for ocular surface protection, with evident improvement of the signs associated with dry eye disease. Thus, to health care practitioners and patients, Systane Ultra and Systane Balance represent a good option for the management of dry eye, and in particular, Systane Balance provides the benefit of restoring the thickness of the tear film lipid layer in patients with dry eye secondary to meibomian gland dysfunction.

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Disclosure

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