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REVIEW

A Decade of Effective Dry Eye Disease Management with Systane Ultra (Polyethylene Glycol/Propylene Glycol with Hydroxypropyl Guar) Lubricant Eye Drops

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Abstract: Dry eye disease (DED) is a multifactorial ocular condition characterized by a loss of homeostasis of the tear film resulting in ocular symptoms of discomfort, irritation, and visual disturbance, all of which significantly impact the patients' social and occupational quality of life. While management of DED depends on the severity of symptoms and signs, use of artificial tear products (ATPs) that replace or supplement the deficient natural tear film is the mainstay treatment option. In this review, we present a decade of evidence on Systane Ultra® (polyethylene glycol [PEG]/propylene glycol [PG] with hydroxypropyl guar [HP guar]) in effectively managing DED. The active demulcents in Systane Ultra®—PEG, PG, along with HP guar gelling technology—provide optimal ocular surface protection and lubrication to heal damaged areas of the cornea caused by DED and, therefore, are recommended for patients with both aqueous and/or mucin layer deficiencies. Over the years, several clinical studies have shown that PEG/PG with HP guar provides long-lasting relief from dry eye and has often been chosen as a standard or comparator against other ATPs. Here, we describe the salient features of PEG/PG with HP guar—its constituents and their mechanisms of action. Furthermore, we summarize results from a systematic literature search that identified 23 relevant publications further emphasizing on the effectiveness and safety of PEG/PG with HP guar in alleviating the signs and symptoms of DED.

Keywords: artificial tear products, dry eye disease, PEG/PG with HP guar

Dry Eye Disease: Prevalence, Definition, Burden, and Management

Dry eye disease (DED), also known as keratoconjunctivitis sicca, is a critical and significant public health issue affecting ~344 million people worldwide and more than 30 million in the United States alone [https://www.tfosdewsreport.org/, last accessed 10 February 2020]. The estimated prevalence of DED ranges from 5% to 34% in individuals over 50 years old and is more common in women; however, with increased use of electronic/media devices the risk of DED in the younger population is on the rise.[1,2]

In 2017, the Tear Film & Ocular Surface Society's Dry Eye Workshop II (TFOS DEWS II) report defined DED as a "multifactorial disease of the tears and ocular surface that results in symptoms of discomfort, visual disturbance, and tear film instability with potential damage to the ocular surface". It is accompanied by

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increased osmolarity of the tear film and inflammation of the ocular surface.[3,4] Patients with DED may complain of ocular discomfort including redness, burning and stinging, ocular dryness, photophobia, foreign body sensation, grittiness, and visual disturbance, all of which significantly affect the quality of lives of patients (reporting up to 34% impairment in daily activities).[5,6] Etiologically, DED is classified into (i) aqueous-tear deficiency, characterized by lack of tear secretion from the lacrimal glands, and (ii) evaporative DED, involving excessive evaporative loss of tears due to meibomian gland deficiencies.[2] However, most DED (>80%) are mixed conditions characterized by both lacrimal and meibomian gland deficiencies.[7]

With the increasing burden of DED and its impact on patients' daily and social lives that worsens with age, it is important to manage this condition appropriately.[4] Depending on severity of the disease, the treatment and management of DED include patient education (about the condition, management, and prognosis); modifications in the environmental, dietary, and lifestyle-related factors; artificial tear substitutes; punctal plugs; lid warming and intranasal stimulation devices; topical and/or systemic anti-inflammatory medications, such as cyclosporine, diquafosol, and lifitegrast; and surgery.[8] Treatment goals include relieving the signs and symptoms of the disease, improving patients' comfort, re-establishing ocular surface homeostasis, and minimizing corneal damage.[7,9] Irrespective of the severity grade of DED, over-the-counter (OTC) eye drops, or artificial tear products (ATPs) are the mainstay and first-line treatment for DED providing immediate symptomatic relief.[4,10]

Artificial Tear Products

ATPs are lubricant eye drops used to treat the dryness and irritation associated with DED. These buffered formulations, with or without preservatives, contain electrolytes, surfactants, and one or more lubricants that may be guar- or cellulose-based derivatives including hydroxypropyl guar (HP guar), glycerin, dextran, polyvinyl alcohol, polyethylene glycol [PEG] 400, propylene glycol [PG], sodium hyaluronate, and polyvinylpyrrolidone to enhance or replace the tear film.[8–12]

The numerous commercially available ATPs are primarily hypotonic or isotonic buffered solutions containing other excipients (eg, electrolytes, surfactants, and various types of viscosity agents). Most target to replenish either the aqueous or lipid layer of the tear film and there is no consensus on the therapeutic efficacy of one over the other.[13] The ideal artificial tear is one that can spread uniformly and evenly, minimize friction during blinks, has minimal blurring upon instillation, is safe and convenient to use, and effectively improves the signs and symptoms of dry eye.[12] Further, an ideal ATP should also have the potential to restore deficiencies in both, aqueous and lipid, layers of the tear film to address patient's dry eye symptoms, regardless of the deficiency (lacrimal or meibomian) within the tear film that may be causing the symptoms.

Here, we describe the constituents, mechanisms of action, and clinical evidence of PEG/PG with HP guar that is formulated with an intelligent delivery system and offers symptomatic relief to consumers/patients across the wide spectrum of DED.

Systane Ultra (PEG/PG with HP GUAR)

Systane Ultra® (PEG/PG with HP guar; Alcon, Fort Worth, TX, USA) has been commercially available since 2008. PEG/PG with HP guar is commercially available in several countries across four markets (Asia-Pacific, Europe/Middle East/Africa, Latin America/Caribbean, and North America) worldwide, and provides immediate comfort, extended ocular surface protection, and symptom relief for DED due to insufficient quantity or quality of natural tears.[14]

Formulation

The active ingredients of PEG/PG with HP guar lubricant eye drops are the hydrophilic demulcents 0.4% PEG 400 and 0.3% PG, which have lower viscosity than cellulose derivatives.[14] The lubricant drops also contain HP guar, a natural polysaccharide gelling agent, and are buffered with borate and sorbitol. Moreover, these lubricant formulations containing PEG/PG with HP guar are free of preservatives.

HP Guar

The HP guar technology was originally developed for ophthalmic use in contact lens multi-purpose solutions (UNIQUE pH™, Alcon Laboratories, Inc., Fort Worth, Texas, USA). Use of HP guar, a water-soluble natural polysaccharide excipient, in PEG/PG with HP guar lubricant drops increases the viscosity of the eye drop owing to its high molecular weight (1000–5000 kDa).[8,12,14]

Although Systane Ultra and Systane Original have similar HP guar concentrations and 2-hour viscosities

(range, 4300–5800 Cps), the pH of Systane Ultra (pH 7.9) is higher than that of Systane Original (pH 7.0). Moreover, sorbitol is included in Systane Ultra but not in Systane Original. Upon exposure to the higher pH (~7.5) of the ocular surface and tears, HP guar's interaction with borate and divalent ions in the tear film allows the formation of the protective viscoelastic matrix on the ocular surface to provide prolonged retention of the active demulcents, thereby protecting the ocular surface. Further, this gel matrix mimics the mucin in the tear film and reduces the friction between the eyelid and ocular surface during blinks.[8,12,14]

HP guar molecules preferentially bind to desiccated or damaged hydrophobic regions of the cornea; this allows protective layer to limit further damage and time for surface epithelial cells to undergo repair and renewal.[14–16] A preclinical study using in vivo (desiccated corneas of anesthetized rabbits) and in vitro (immortalized human corneal epithelial cells and Chang conjunctival cells) models, based on methylene blue uptake, showed that HP guar, PEG, and PG effectively and uniformly formed a layer on the ocular surface providing protection from desiccation, thereby allowing recovery of the damaged epithelium.[16] In another preclinical in vivo study, the effect of lubricant drops containing PEG/PG with HP guar on precorneal mucous layer was evaluated over 7 days in New Zealand white rabbits (N = 16).[17] Their right eyes were treated with PEG/PG/HP guar and the left eyes were randomized to receive PEG/PG/HP guar with Polyquad, 0.1% hyaluronate sodium, 0.5% carboxymethyl cellulose (CMC), and phosphate-buffered saline. The study showed a significantly thicker mucous in eyes treated with PEG/PG/HP guar drops compared with PEG/PG/HP guar with Polyquad ($P< 0.001$ vs all). Interestingly, no significant difference was noted in the mucous layer between the eyes treated with PEG/PG/HP guar and PEG/PG/HP guar with Polyquad.[17]

In a clinical study of 87 patients with DED, Christensen et al[15] demonstrated that, compared to control (CMC sodium; Refresh Tears® Lubricant Eye Drops, Allergan, Irvine, CA, USA), PEG/PG with HP guar lubricant significantly reduced conjunctival ($P= 0.025$) and temporal corneal staining ($P= 0.024$). Furthermore, patients reported a reduction in DED symptoms in the morning ($P= 0.015$) and evening ($P= 0.023$), lower frequencies of foreign body sensation ($P= 0.033$), and felt their eyes were "refreshed longer" ($P=0.037$); thereby confirming that PEG/PG with HP guar lubricant drops were more effective at alleviating signs and symptoms of dry eye than CMC sodium alone (Refresh Tears).[15]

Tear instability and increased evaporation in all types of DED results in tear film hyperosmolarity (one of the key characteristics of the disease). A clinical study by Ng et al[18] in 31 patients with DED (with Ocular Surface Disease Index questionnaire [OSDI] ≥20 and mean tear osmolarity ≥300 mOsm/L in at least one eye) showed that treatment with PEG/PG with HP guar for 3 weeks (4 times/day [QID] for 3 weeks) showed a significant reduction in tear osmolarity scores (mean, standard deviation [SD]: 314.6 [11.9] mOsm/L vs 307.7 [15.7] mOsm/L, $P< 0.05$) compared to baseline. Furthermore, significant improvements were observed in dry eye conditions and symptoms at Week 3 (mean OSDI score: $P\leq 0.01$; non-invasive tear break-up time [NIBUT]: $P< 0.05$; central corneal staining: $P< 0.05$) from baseline. The study further noted that, unlike other hypotonic drops, the reduction in tear osmolarity was observed even 15 minutes after instillation with PEG/PG with HP guar.[18]

In 2015, a pre-clinical study by Rangarajan et al explored a potential synergistic benefit of combining HP guar with another naturally viscoelastic hydrophilic polymer, hyaluronic acid (HA), that has also been shown to reduce ocular surface damage in DED patients.[19,20] It was observed that in human corneal epithelial cells, hydration protection against desiccation and protection by surface retention were significantly greater with HA/HP guar vs HP guar or HA alone ($P< 0.001$). Also, protection with HP guar alone was significantly greater vs HA alone ($P=0.016$). Post surfactant-insult, cell viability, cell barrier protection, tissue hydration, and lubricity were also significantly greater with dual-polymer formulation than HP guar or HA alone.[20] Overall, these findings confirm that HP guar in lubricant eye drops improves the adherence and retention of the ATP, improves tear stability and tissue hydration, and minimizes tear evaporation, thereby lowering tear osmolarity and corneal dryness to provide long-lasting relief from DED symptoms.

Preservatives in PEG/PG with HP Guar

The treatment options for DED are constantly evolving; however, use of lubricant eye drops is a constant through different stages of the disease to provide symptomatic relief. With the long-term and continuous usage of these lubricant drops, the ATPs should be sterile to prevent unwanted effects on the ocular surface, and hence preservatives are added to ATP formulations for their

antimicrobial properties.[21,22] Furthermore, considering the long-term and frequent usage of the ATPs, it is important that the preservatives added to the ATPs are well tolerated with minimal or no side effects.[21]

The most commonly used preservative in prescription topical ophthalmic drops, including ATPs, is benzalkonium chloride (BAK), which demonstrates pan-antimicrobial properties; however, BAK-containing formulations have shown to have deleterious effects on the ocular surface and are not widely used in OTC ocular lubricants or artificial tears.[21–23] Over the last decade, PEG/PG with HP guar lubricant eye drops have shown to provide relief from the symptoms of dry eye without the use of certain preservatives that have adverse effects. Unlike many OTC eye drops, the preservative used in PEG/PG with HP guar is polyquaternium or Polyquad, a hydrophilic cationic polymer that was initially developed and used as an antimicrobial disinfectant in contact lens solutions. The large molecular size of Polyquad is key to its function, while it effectively disrupts microbial membranes, its sheer size exclusion prevents cytotoxicity in mammalian cells.[21,24] Polyquad has shown to be effective against *Pseudomonas aeruginosa, Serratia marcescens, Staphylococcus aureus*, and the fungus *Candida albicans*.[25] With more than 30 years of usage, safety concerns raised with Polyquad are minimal – it does not adversely affect the ocular surface and has shown to offer comparable tolerability to a preservative-free eye drops.[17,21,22]

The concerns over the use of preservatives in ATPs, in addition to physician and patient preferences, have led to the development of preservative-free formulations. While preservative-based eye drops have a longer shelf life, preservative-free drops typically come in disposable single-dose sterile vials that reduce the risk of contamination and eliminate the need for preservatives. PEG/PG with HP guar preservative-free lubricant eye drops relieve dry eye symptoms with a preservative-free formula and are available in convenient, single-use sterile vials that provide immediate and long-lasting DED symptom relief similar to its preserved formulation.[17] Lubricant eye drops are now also available in multi-dose preservative-free formulations that are cost effective and easy to use.[21,22,26]

Mechanism of Action

PEG/PG with HP guar lubricant eye drops are maintained at a pH of 7.9 where HP guar, borate, and sorbitol exist in a state of dynamic equilibrium where sorbitol optimizes the viscosity of the drop.[12] During instillation, the pressure exerted on the bottle reduces the drop viscosity and once instilled, the concentration of sorbitol decreases owing to its water solubility, allowing for efficient and uniform spreading. The borate ions in Systane interact with galactomannan on the surface of the eye to form a protective cross-linked bio-adhesive gel.[12,14,27] Further, the ionic properties of the tear film increase the density of the borate/HP guar crosslinks and fortify this low viscosity gel matrix to allow retention of active demulcents for tear film stability and lubrication, decrease evaporation of the tear film, and protect the ocular surface (Figure 1). The borate/HP guar gel matrix also reduces friction between blinks to provide prolonged relief and comfort.[14]

The aforementioned properties make PEG/PG with HP guar an ideal lubricating drop with a longer retention time and sustained lubrication for aqueous-deficient, evaporative, and mixed DED conditions.

Clinical Studies of PEG/PG with HP Guar

A literature search was conducted independently by the authors on the PubMed database; following removal of duplicates, a total of 304 articles were identified using

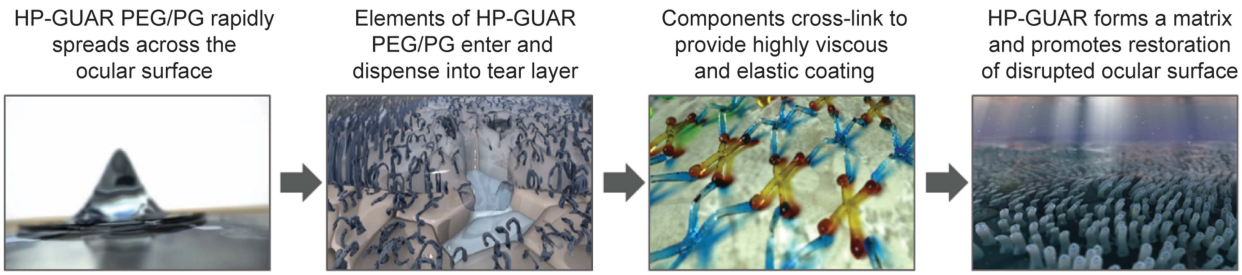

Figure 1 Mechanism of action of PEG/PG with HP GUAR. Image courtesy with permission from Alcon.
Abbreviations: HP GUAR, hydroxypropyl-guar; PEG, polyethylene glycol; PG, propylene glycol.

the following search strings: (i) (Systane Ultra) AND (dry eye disease OR DED OR dry eye syndrome OR DES or dry eye); (ii) ([polyethylene glycol OR PEG] AND [propylene glycol OR PG] AND [hydroxypropyl guar OR HP guar OR HPG]) AND (dry eye disease OR DED OR dry eye syndrome OR DES or dry eye); (iii) (Systane Ultra) AND (artificial tears OR ocular lubricants OR lubricant eye drops OR ATP); (iv) ([polyethylene glycol OR PEG] AND [propylene glycol OR PG] AND [hydroxypropyl guar OR HP guar OR HPG]) AND (artificial tears OR ocular lubricants OR lubricant eye drops OR ATP); and (v) (dry eye OR DED) AND (artificial tears AND lubricant). Multiple reports of the same dataset were assessed, and only the most updated articles were included. Only English language articles were included. Abstracts retrieved from the search were screened and a total of 20 relevant articles were identified, with consensus, by the authors were further evaluated and reviewed. In addition, 3 relevant abstracts on the use of PEG/PG with HP guar in DED identified from Google Scholar Search were also identified and reviewed. Data from the studies reporting on the use of PEG/PG with HP guar in dry eye conditions, including the study design, patient population, lubricant dosage, and endpoints assessed are summarized in Figure 2.

Over the last 10 years, clinical studies have demonstrated that the use of PEG/PG with HP guar is associated with improvements in the signs and symptoms of dry eye and is well tolerated in patients with DED (Table 1). Here, we present an overview of key clinical studies conducted with PEG/PG with HP guar in patients with dry eye.

Efficacy and Safety of PEG/PG with HP Guar (Systane Ultra)

A 6-week, controlled, randomized, prospective, double-masked, multisite, parallel-group study conducted by Davitt et al[28] on 113 patients with DED evaluated the efficacy and safety of PEG/PG with HP guar (vs saline) in improving the signs and symptoms of DED. The study demonstrated a reduction in the severity of dry eye with no untoward safety issues.[28] Use of PEG/PG with HP guar lubricant eye drops reduced both corneal and conjunctival staining as early as Day 7, with significant reduction in mean corneal staining (P= 0.0009) by Day 14 and in mean conjunctival staining (P= 0.0475) by Day 28 that was sustained until end of the study. Furthermore, with PEG/PG with HP guar use patients also reported significant reductions in the mean scores for the ocular symptoms of dryness and OSDI vs baseline. The authors concluded that PEG/PG with HP guar lubricant was efficacious and well tolerated when used QID for 6 weeks in patients with dry eyes.[28]

The efficacy of ATPs in relieving symptoms of dry eye typically rely on patient reporting, which may be subjective.[29] Therefore, in addition to patient-reported scores, clinicians evaluate signs of ocular damage by staining for specific ocular surface antigens that are altered during DED. Human leukocyte antigen-*DR* isotype (HLA-DR) is one such biomarker for increased inflammation on the ocular surface associated with DED.[30,31] Fernandez et al[32] showed that treatment with PEG/PG with HP guar for 30 days significantly reduced HLA-DR expression (P= 0.02), corneal staining (P= 0.01), OSDI score (P= 0.02), and tear firm breakup time (TFBUT; P= 0.01), suggesting a reduction in surface inflammation and thereby an improvement in the signs and symptoms of DED.

In 2017, Labetoulle et al[33] demonstrated that PEG/PG with HP guar decreased ocular surface staining based on the mean change in total ocular surface staining (TOSS) score from baseline at Day 35 (mean [SD]: −2.2 [0.33] points), thereby alleviating the signs and symptoms in patients with DED. Further, patient-reported scores from the study indicated that DED treatment with PEG/PG with HP guar was effective, convenient, and well tolerated over 3 months of treatment.[33] Asbell et al[34] showed that PEG/PG with HP guar eye drops instilled QID or PRN to DED patients (N = 97) reduced corneal staining but the difference between the two dosing regimens for reduction in TOSS score was not statistically significant (mean [SD]: −1.19 [0.26] for QID vs −0.94 [0.24] for PRN; P= 0.184). However, the Impact of Dry Eye on Everyday Life (IDEEL) symptom-bother score favored QID dosing, suggesting that the regular use of artificial tears may provide improved symptom relief vs PRN use in DED. Overall, both regimens were well tolerated with no new safety findings.[34]

As mentioned earlier, Ng et al showed a significant (P< 0.05) reduction in osmolarity (15 minutes after instillation), in addition to improvements in dry eye symptoms (conjunctival hyperemia, ocular surface staining, and central corneal staining) using PEG/PG with HP guar QID over 3 weeks in DED patients (N = 31).[18] More recently, a study by Aguilar et al[35] demonstrated the efficacy of PEG/PG with HP guar (thrice daily) at Day 90 (vs baseline) in reducing squamous metaplasia (based on mean ± SD goblet cell density score: 0.8 ± 0.5 vs 1.2 ± 0.5; P<

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