

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 al¹⁵ 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 al¹⁸ 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}

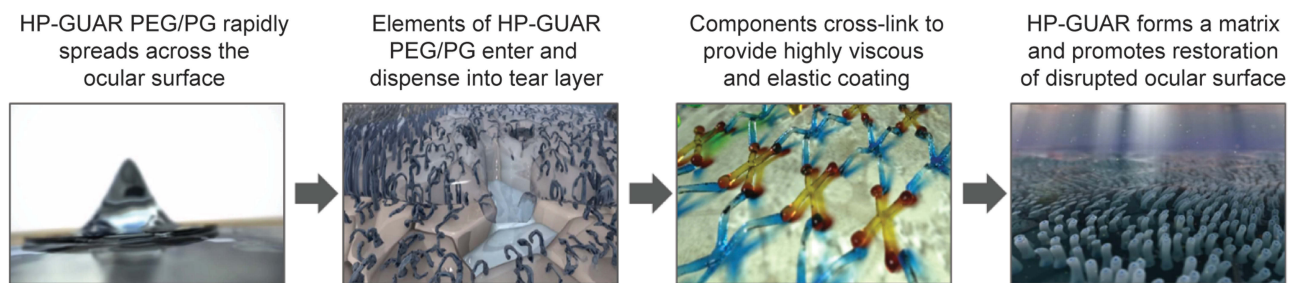
Mechanism of Action

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



HP-GUAR: hydroxypropyl-guar; PEG: polyethylene glycol; PG: propylene glycol

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 al²⁸ 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 al³² 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 film 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 al³³ 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 al³⁴ 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 al³⁵ demonstrated the efficacy of PEG/PG with HP guar (thrice daily) at Day 90 (vs baseline) in reducing squamous metaplasia (based on mean \pm SD goblet cell density score: 0.8 ± 0.5 vs 1.2 ± 0.5 ; $P<$

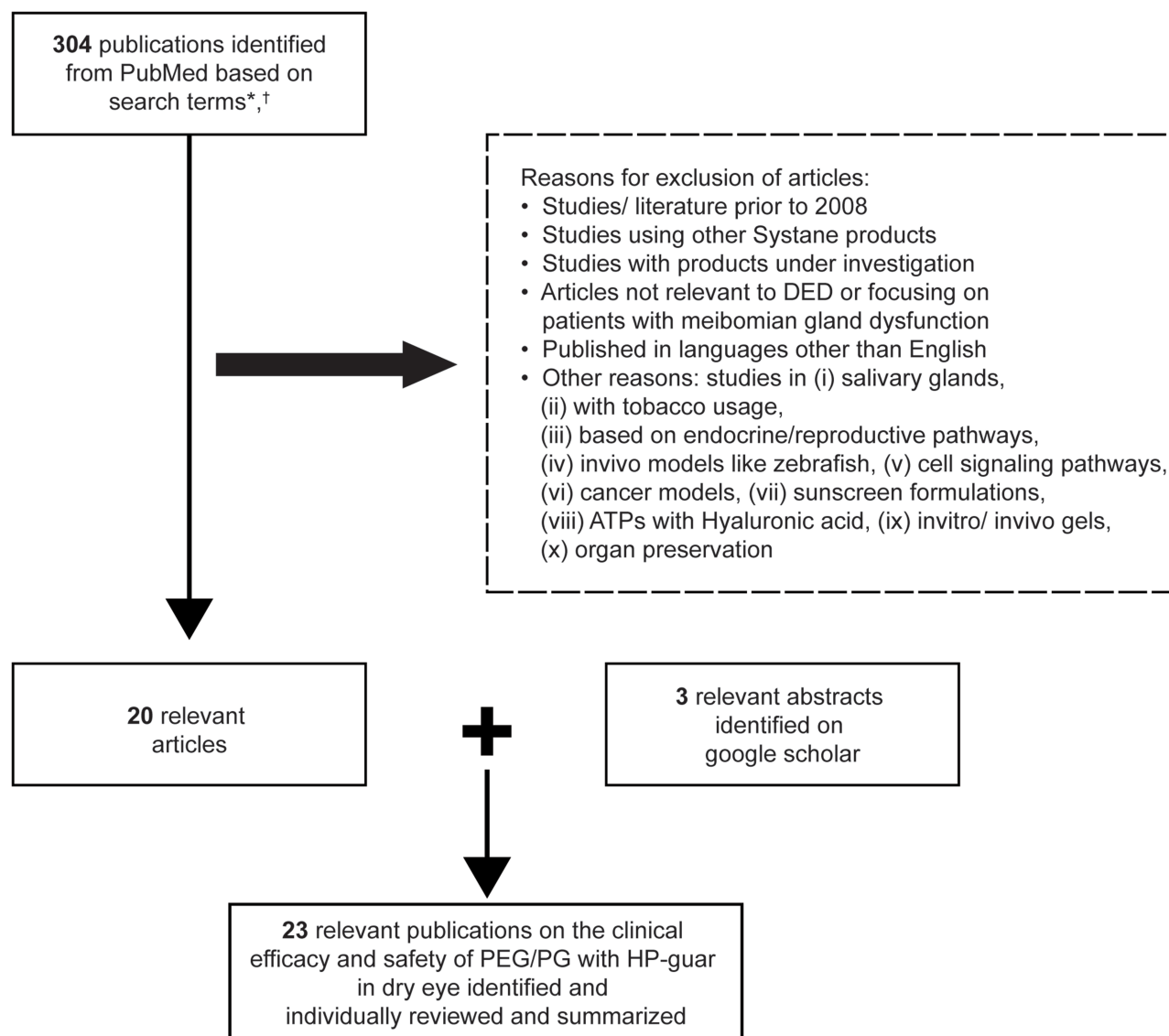


Figure 2 Flow chart for literature search for publication screening and inclusion. *Search strings used: (i) (Systane Ultra) AND (dry eye disease OR DED OR dry eye syndrome OR DES or dry eye); (ii) ([polyethylene glycol OR PEG] AND [propylene glycol OR PG] AND [hydroxypropyl guar OR HP guar OR HPG]) 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). †After removing duplicates.

0.0001), improving TFBUT (6.8 vs 5.8; $P < 0.0001$), corneal staining (0.3 vs 3.1; $P < 0.00010$), and conjunctival staining (0.9 vs 3.6; $P < 0.0001$), thereby allowing normalization of the ocular surface in patients with DED.

Comparator Studies: PEG/PG with HP Guar vs Other ATPs/Treatments

With more than a decade of effectively alleviating the signs and symptoms of dry eye without any major safety concerns, PEG/PG with HP guar is frequently used as

a standard/comparator while assessing the effectiveness of other lubricant eye drops in DED.

PEG/PG with HP Guar vs Optive

PEG/PG with HP guar has been compared with Optive[®] Tears (CMC and glycerin; Allergan; <https://www.allergan.com.au/en-au/products/list/optive-lubricant-eye-drops-15mL>, last accessed 07-February 2020) across four different studies.^{28,33,36,37}

Davitt et al²⁸ were the first to compare the efficacy and safety of PEG/PG with HP guar with that of Optive in

Table I Clinical Studies Using PEG/PG with HP Guar Lubricant Eye Drops in DED

Publication	No. of DED Patients Treated with PEG/PG with HP-Guar	No of Patients Treated with Comparator	Endpoints	Results
Davitt et al, 2010 ²⁸	n = 52	Optive (CMC/glycerin) n = 53	Corneal staining	P < 0.0009 at day 14; P = 0.0106 at day 42 compared with Optive
			Conjunctival staining	P = 0.0475 at day 14; P = 0.00009 at day 42 compared with Optive
			Ocular symptoms score	No significant differences between groups
			TFBUT	
			OSDI scores	
			VF-14 scores	
Fernandez et al, 2015 ³²	n = 16 moderate-to-severe DED	None	Corneal staining	P < 0.0001 relative to baseline
			Conjunctival staining	No change
			TFBUT	P < 0.0001 relative to baseline
			DEWS score	P < 0.0001 relative to baseline
			OSDI score	P = 0.02 relative to baseline
			Cells expressing HLA-DR	P = 0.02 relative to baseline
Labetoulle et al, 2017 ³³	n = 43	Optive (osmoprotective CMC/glycerin) n = 41	TOSS score	No significant differences between groups
			IDEEL score	
Asbell et al, 2018 ³⁴	N = 97 drop 4x/day (n = 34) vs as needed (n = 63)	None	TOSS score	No differences between groups
			IDEEL score	
Ng et al, 2018 ¹⁸	n = 28	None	Tear osmolarity	P < 0.05 relative to baseline in worse eye
			NITBUT	
			Corneal staining	
			Conjunctival hyperemia	Improvements not significant
			Conjunctival staining	
Aguilar et al, 2018 ³⁵	n = 49	None	Goblet cell density	P < 0.0001 at days 30, 60, 90 relative to baseline
			Corneal staining	
			Conjunctival staining	
			TFBUT	

(Continued)

Table I (Continued).

Publication	No. of DED Patients Treated with PEG/PG with HP-Guar	No of Patients Treated with Comparator	Endpoints	Results
Torkildsen, 2009 ³⁶	N = 48	Optive (osmoprotective CMC/glycerin) n = 48 Crossover study	IVAD	P = 0.0365 at 90 min compared with Optive
			Median time at BCVA	No significant differences between groups
			Reading rate	
			Functional blink rate	
Guillon et al, 2011 ³⁷	N = 27	Optive (osmoprotective CMC/glycerin) n = 27	VA	Superior to comparator in static and time-controlled visual performance for high-contrast optotypes
			OSDI scores	No significant differences between groups
			Subjective vision scores	
			Subjective comfort scores	
Torkildsen et al, 2017 ³⁸	N = 41	Rohto (PG/povidone) n = 39	Ocular comfort scores	No significant differences between groups
			Corneal staining	
			Conjunctival staining	
			TFBUT	
			Ora Calibra Ocular Discomfort Scale	
			4-Symptom Questionnaire	
			Ora Calibra Quality of Life Questionnaire	
Corcoran et al, 2017 ³⁹	N = 33 (+15 without DED)	Rohto (PG/povidone) n = 33 (+15 without DED)	Cooling score	No significant differences between groups
			Corneal staining	
			Schirmer's score	
			OSDI	

(Continued)

Table I (Continued).

Publication	No. of DED Patients Treated with PEG/PG with HP-Guar	No of Patients Treated with Comparator	Endpoints	Results
Kislan, 2010 ⁴⁰	n = 40	Blink Tears (PEG) n = 40 crossover study	TBUT	Compared with baseline, Blink Tears significant improved TBUT (P = 0.003), but ULTRA did not (P = 0.320)
			Vision and blurring	Blink was more soothing and less blurring, as well as showing more improved vision and comfort (P < 0.043) than ULTRA
			Soothing and comfort	
Waduthantri et al, 2012 ⁴¹	N = 15	Refresh (PEG/PG) N = 15	SANDE score	No significant differences between groups
			Corneal staining	
			TFBUT	
			Schirmer's test	
Wong et al, 2017 ⁴³	n = 20	Optimel (Manuka (Leptospermum sp.) honey eye drops) n = 20 Crossover study	TFBUT	No significant differences between groups
			Conjunctival staining	
			Ocular comfort index	P = 0.05
			OSDI	P = 0.02
Maharana et al, 2017 ⁴⁴	n = 48	0.5% Carboxymethyl cellulose (CMC), n = 41 0.3% hydroxypropyl methylcellulose (HPMC), n = 31	OSDI	ULTRA superior to CMC but similar to HPMC at weeks 1 and 4
			TBUT	
			Schirmer's test	
Kading, 2010 ⁴⁶	N = 45 contact lens wearers PEG/PG with HP-guar (n = 23)	Sensitive Eyes (n = 22)	Corneal staining	No significant differences between groups
			VA	
McDonald et al, 2014 ⁴⁵	n = 89 contact lens wearers PEG/PG with HP-guar (n = 44)	No treatment (n = 45)	Increased comfortable wear time	P = 0.078 compared with no treatment
			End of day comfort	P = 0.007 compared with no treatment
			Overall dryness	P < 0.001 compared with no treatment
			End of day dryness	P = 0.04 compared with no treatment

(Continued)

Table I (Continued).

Publication	No. of DED Patients Treated with PEG/PG with HP-Guar	No of Patients Treated with Comparator	Endpoints	Results
Gokul et al, 2017 ⁴⁷	n = 30 Systane Ultra applied to one eye; Systane Balance (PG + HP-guar) applied to the other eye	Systane Balance (PG + HP-guar)	Low contrast glare acuity	Significantly more improved in the Balance than in the Ultra group
			Lipid layer grade	
			NIBUT	
			Ocular comfort	
			Temperature variation factor	No changes
Tear meniscus height				
Bitton et al, 2018 ⁴⁸	n = 18 PEG/PG with HP-guar instilled at ambient temperature and after refrigeration		Comfort level	No effect of temperature
Labiris et al, 2017 ⁵⁰	N = 180 following cataract surgery Fixed combination of tobramycin and dexamethasone (FCTD) for 3 wks followed by PEG/PG with HP-guar for 6 wks (n = 59)	FCTD for 3 wks followed by 0.1% hyaluronate for 6 wks (n = 60) or FCTD alone for 3 wks (control group; n = 61)	TFBUT	Better in both study groups than in the control group at all time points; no differences between the two study groups
			Foreign body sensation	
			Subjective discomfort index	
			Blinking discomfort	Better in both study groups at wk 1
			Stinging sensation	No significant differences among the 3 groups
			Tearing sensation	
			Subjective discomfort index	
			Central corneal thickness	
Central corneal sensitivity				

Abbreviations: CMC, carboxymethyl cellulose; DED, dry eye disease; DEWS, Dry Eye WorkShop; HLA-DR, human leukocyte antigen D-related; IVAD, interval visual acuity decay; N, total number of subjects; n, number of subjects; NIBUT, non-invasive tear break-up time; OSDI, ocular surface disease index; SANDE, Symptom Assessment in Dry Eye; TFBUT, tear firm breakup time; TOSS, total ocular surface staining; VA, visual acuity.

adult patients with dry eye (N = 105). No differences were observed between the two products with respect to symptomatic relief (treatment satisfaction, post-treatment ocular symptom scores, or OSDI outcomes). However, patients treated with PEG/PG with HP guar had significantly lower mean corneal staining at Days 14 ($P=0.0009$) and 42 ($P=0.0106$) and significant reductions in conjunctival staining at Days 28 ($P=0.0475$) and 42 ($P=0.0009$).²⁸ A more recent study by Labetoulle et al³³ demonstrated that PEG/

PG with HP guar was non-inferior to Optive based on mean change in TOSS score from baseline to Day 35 (mean \pm SD: -2.2 ± 0.33 [PEG/PG with HP guar] vs -1.7 ± 0.47 [Optive]; $P=0.38$). Both treatments improved ocular surface health, alleviated signs and symptoms of dry eye, and had similar patient-reported scores for treatment effectiveness (62.2 [PEG/PG with HP guar] vs 55.7 [Optive]) and inconvenience (69.5 [PEG/PG with HP guar] vs 67.1 [Optive]).³³

Two independent studies evaluated the effect of PEG/PG with HP guar vs Optive on visual function. The first, conducted in patients with DED (N = 48), showed that PEG/PG with HP guar improved maintenance of visual acuity (VA; as measured by the Interval Visual Acuity Decay [IVAD] test) between blinks at 90 minutes post-instillation vs Optive ($P=0.0365$).³⁶ Overall, both PEG/PG with HP guar and Optive were well tolerated, with no significant differences between mean scores reading rate ($P=0.38$) and functional blink rate ($P=0.15$).³⁶ A study by Guillon et al³⁷ compared the effect of PEG/PG with HP guar vs Optive on visual performance. The results showed that, in patients with mild-to-moderate DED (N = 54), both PEG/PG with HP guar and Optive provided significant improvements in patient-reported vision and comfort with relieved symptoms ($P<0.001$). Furthermore, repeated usage of PEG/PG with HP guar provided beneficial effects with respect to visual performance.³⁷

PEG/PG with HP Guar vs Rohto

Thus far, two studies have compared PEG/PG with HP guar with Rohto[®] (The Mentholatum Company, Orchard Park, NY, USA, <http://www.rohtoeyedrops.com/professionals/>, last accessed 07 February, 2020) lubricant drops, where PEG/PG with HP guar was used as a -comparator.^{38,39} Rohto is a sterile, buffered product packaged in a multi-dose container containing propylene glycol and povidone in a clear microemulsion formulation. In a prospective, double-blind, crossover study in normal and DED patients, Corcoran et al³⁹ showed that mean corneal sensitivity scores were equivalent and normal in both patient groups at baseline and 10 min after instillation of Rohto Hydra and PEG/PG with HP guar ($P=0.24$). Mean cooling scores post Rohto Hydra and PEG/PG with HP guar instillation was higher in DED patients vs normal at all assessed time points. While sum cooling scores with both lubricant drops were significantly higher in DED patients vs normal, cooling response with Rohto Hydra was greater vs PEG/PG with HP guar only in the DED group (DED: $P=0.004$; normal: $P=0.320$).³⁹ Torkildsen et al³⁸ showed that both lubricant drops (administered twice-a-day) were comparable in improving the signs and symptoms of DED over the 4-week assessment period based on ocular staining, tear film metrics, ocular comfort ($P=0.364$), and visual function assessments. Based on the quality of life questionnaire, improvements in three of four metrics, including driving, were greater

for the Rohto users, but the differences were not statistically significant.³⁸

PEG/PG with HP Guar vs Blink Tears

In patients with mild-to-moderate DED (N =40), Blink Tears[®] (polyethylene glycol [PEG], Johnson & Johnson, <https://www.justblink.com/find-your-products/dry-eye-lubricating-eye-drops/blink-tears-lubricating-eye-drops?upcean=329943002156>, last accessed 07 February, 2020) significantly improved TBUT after 1 month of treatment ($P=0.003$) and no significant changes were noted for staining or VA. Patients reported that Blink Tears was more soothing, improved vision, resulted in less blurring, and was more comfortable than PEG/PG with HP guar ($P<0.043$).⁴⁰

PEG/PG with HP Guar vs Refresh

Thus far, two studies have compared the efficacy of PEG/PG with HP guar and Refresh tears (CMC sodium).^{41,42} In 2012, Waduthantri et al⁴¹ compared the efficacy of Refresh vs PEG/PG with HP guar in Chinese patients with DED (N =30). They demonstrated that there was no significant difference in the efficacy of these drugs in terms of improving symptoms and altering objective signs of dry eye, such as corneal fluorescein staining, TBUT, and Schirmer's test results ($P>0.05$).⁴¹ In an in vitro comparative toxicity study of preservative vs preservative-free ATPs, preservative-free formulations were less cytotoxic to cultured corneal epithelial cells vs their preservative-containing counterparts. While ATPs with preservatives including PEG/PG with HP guar, Blink, and GenTeal[®] (hydroxypropyl methylcellulose 0.3%; Novartis, Novartis [India] Ltd) demonstrated the most in vitro cytotoxicity, non-preserved Refresh Preservative-Free lubricant drops were least cytotoxic to cultured corneal epithelial cells.⁴²

PEG/PG with HP Guar vs Optimel

Wong et al⁴³ demonstrated that in 24 patients with contact lens-related DED, treatment with both PEG/PG with HP guar and Optimel[®] (Manuka honey; Melcare Biomedical Pty Lt, Queensland, Australia) improved DED symptoms. However, comparison of the two lubricant drops demonstrated treatment differences between Optimel and PEG/PG with HP guar based on OSDI ($P=0.02$) and ocular comfort index ($P=0.05$) scores.⁴³

PEG/PG with HP Guar vs Genteal Eye Drops

A retrospective analysis was conducted by Maharana et al⁴⁴ on patients with DED to compare the efficacy of CMC (4X day), PEG/PG with HP guar (2X day), and Genteal Eye Drops. The results demonstrated that patients treated with PEG/PG with HP guar demonstrated significant improvements in mean OSDI ($P=0.0$), TBUT ($P\leq 0.01$), and in Schirmer's test ($P\leq 0.02$) vs those treated with CMC at all assessed follow-up time points (0–1, 0–4, and 1–4 weeks). No significant difference was noted for OSDI, TBUT, and Schirmer's test assessments between patients treated with PEG/PG with HP guar and those treated with HPMC 0.3%.⁴⁴

PEG/PG with HP Guar is Well Tolerated in Contact Lens Wearers

Contact lens wear is often associated with symptoms of ocular irritation, including symptoms of dryness, discomfort, soreness, and tiredness. Among contact lens wearers, 25% to 50% suffer from contact lens-related dry eye.⁴⁵

Kading et al⁴⁶ provided evidence of the safety and compatibility of PEG/PG with HP guar lubricant eye drops in contact lens wearers. They showed that PEG/PG with HP guar usage in contact lens wearers was not associated with any significant change in corneal staining, distance VA, or with any adverse events.⁴⁶ In 2014, McDonald et al⁴⁵ assessed the clinical performance of PEG/PG with HP guar in daily disposable soft contact lens wearers. The study demonstrated that the use of PEG/PG with HP guar over 2 weeks resulted in a significant increase in comfortable lens wear time ($P=0.007$). A significant reduction in overall dryness ($P<0.0001$) and end-of-the day dryness ($P=0.047$) were also observed PEG/PG with HP guar.⁴⁵

Overall, these studies suggest that PEG/PG with HP guar provide extended protection and provide long-lasting relief from dryness symptoms associated with contact lens usage.

PEG/PG with HP Guar Usage Under Environmental Conditions and During/Post-Cataract Surgery

Adverse environmental conditions worsen the signs and symptoms of dry eye. Differences in temperature and humidity may affect the efficacy of ATPs in alleviating DED symptoms.^{3,4} In patients with mild-to-moderate dry

eye symptoms ($N=30$), Gokul et al⁴⁷ showed that a single application of PEG/PG with HP guar had protective effects against exposure to dry conditions. Following exposure to a validated simulated adverse environment model created by a 45 cm 55-W standing fan directed towards the eye, at a distance of 1m for 2.5 minutes, PEG/PG with HP guar increased NIBUT ($P<0.001$) and prevented its decline below baseline.⁴⁷ While the manufacturer's recommendation is to store PEG/PG with HP guar at room temperature, Bitton et al⁴⁸ demonstrated that the effect of PEG/PG with HP guar in providing comfort is the same irrespective of storage temperature. Based on patient-reported outcomes, the study did not reveal any advantage in refrigerating the drops prior to use either in the morning or late in the day in mild-to-moderate DED patients.⁴⁸

In a prospective, parallel, randomized, investigator-masked, single-center, clinical study, Davidson et al⁴⁹ evaluated the efficacy of PEG/PG with HP guar in patients with a history of episodic eye irritation or dryness related to environmental factors seeking routine cataract extraction. They showed that the use of PEG/PG with HP guar (in addition to standard of care) provided ocular surface protection and significant improvements in ocular surface comfort, as well as signs and symptoms of dry eye. Based on these results, the authors suggested that PEG/PG with HP guar might contribute to improvement in post-cataract surgical outcomes.⁴⁹ Further, a comparative study with PEG/PG with HP guar and Hylocomod (Farmex, Greece) in patients who underwent cataract extraction surgery showed that both ATPs provided a significant improvement in TBUT index ($P<0.05$) associated with a reduction in foreign body sensation through the postoperative period and a significant reduction of the blinking discomfort for the first postoperative week.⁵⁰ Overall, the study demonstrated that both PEG/PG with HP guar and Hylocomod were equally efficient in alleviating ocular surface disease symptoms following cataract extraction surgery.⁵⁰

Overall, these clinical studies demonstrate the clinical efficacy and safety of PEG/PG with HP guar in improving the signs of DED while providing lasting relief from symptoms. The interaction between HP guar, borate, and divalent ions in the tear film results in the formation of viscoelastic matrix that allows longer retention of active demulcents and protects ocular surface.^{8,12,14} HP guar molecules form a protective layer around the compromised hydrophobic areas of cornea, which avoids further damage and allows time for repair and lubrication of the surface. Furthermore, the addition of Polyquad, a hydrophilic

cationic polymer, prevents accidental contamination and shown to be effective against *Pseudomonas aeruginosa*, *Serratia marcescens*, *Staphylococcus aureus*, and the fungus *Candida albicans*.²⁵ After more than three decades of usage, the Polyquad is neither associated with any safety concerns nor has adverse effect on the ocular surface.^{17,21,22} Although these unique properties of demulcents and safety and efficacy profile of PEG/PG with HP guar are reported by single arm or comparator studies, it is important to note that this literature review is purely descriptive in nature and we do not intend to draw comparisons with other products. Inter-study differences, including study design, populations, treatment regimens, follow-up period, or statistical methods used for data analysis in publications, may account for the variability observed in the endpoints assessed across these studies. Therefore, comparison of data between different studies may be inconclusive and such be interpreted with caution.

Summary

The presence of lower viscosity demulcents and other excipients (including HP guar and sorbitol) allows PEG/PG with HP guar to form a viscoelastic layer of protection to heal damaged areas of the cornea and to provide extended ocular surface protection and symptom relief. Inclusion of sorbitol PEG/PG with HP guar minimizes blurring. Overall, PEG/PG with HP guar effectively alleviates signs and symptoms of dry eye, including conjunctival and cornea surface staining as well as patient-reported scores for treatment effectiveness and inconvenience. PEG/PG with HP guar has been shown to improve DED symptoms associated with cataract surgery, environmental conditions, and contact lens usage. Clinically, PEG/PG with HP guar lubricant eye drops have been shown to enhance tear film stability, visual function, comfort with contact lens wear, and improved VA in dry eye patients. With over a decade of usage, PEG/PG with HP guar is effective, convenient to use, and well tolerated in DED.

Disclosure

S.S. and V.M. are both employees of Alcon Research, LLC, Johns Creek, Georgia, USA. The authors report no other conflicts of interest in this work.

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