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ADIS DRUG EVALUATION

Perfluorohexyloctane Ophthalmic Solution: A Review in Dry Eye Disease

Amy Zhuang-Yan[1] · **Yahiya Y. Syed**[1]

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Abstract

Perfluorohexyloctane ophthalmic solution (Miebo®) is a single-entity, water-, steroid- and preservative-free, first-in-class semifluorinated alkane that is approved in the USA for the treatment of the signs and symptoms of dry eye disease (DED). DED is often linked with meibomian gland dysfunction (MGD), which causes an excessive evaporation of tears. Perfluorohexyloctane ophthalmic solution stabilizes the lipid layer of the tear film and inhibits tear evaporation by forming a monolayer at the air-liquid interface. In the phase III GOBI and MOJAVE trials in adults with DED associated with MGD, one drop of perfluorohexyloctane ophthalmic solution instilled in each eye four times daily over 8 weeks resulted in statistically significant and clinically meaningful improvements in the signs and symptoms of DED compared with hypotonic saline (0.6%). The agent was generally well tolerated, with most ocular adverse events being mild or moderate in severity. The efficacy and tolerability of perfluorohexyloctane ophthalmic solution was sustained for up to 52 weeks in an extension study (KALAHARI). As the first and currently the only prescription treatment approved in the USA directly addressing the pathophysiology of excessive tear evaporation, perfluorohexyloctane ophthalmic solution is a valuable emerging option for the management of DED.

Plain Language Summary

Dry eye disease (DED) is a common eye disorder caused by many factors. In most cases, DED is linked with meibomian gland dysfunction (MGD), which causes an excessive evaporation of tears. Perfluorohexyloctane ophthalmic solution (Miebo®), a single-entity, water-, steroid- and preservative-free, first-in-class semifluorinated alkane, is approved in the USA for the treatment of the signs and symptoms of DED. The agent stabilizes the lipid layer of the tear film and prevents the evaporation of tears by forming a layer on the surface of the tear film. In two phase III clinical trials in adults with MGD-associated DED, one drop of perfluorohexyloctane ophthalmic solution instilled in each eye four times daily over 8 weeks led to significant improvements in the signs and symptoms of DED when compared with hypotonic saline (0.6%). Perfluorohexyloctane ophthalmic solution was generally well tolerated, with most ocular adverse events being mild or moderate in severity. Thus, as the first and currently the only prescription treatment approved in the USA directly addressing excessive tear evaporation, perfluorohexyloctane ophthalmic solution is a valuable emerging option for the management of DED.

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The manuscript was reviewed by: ***E. Anastasopoulos***, 2nd Department of Ophthalmology, Aristotle University of Thessaloniki, Thessaloniki, Greece; ***F. Hakim***, Department of Ophthalmology, University of Michigan, Ann Arbor, MI, USA; ***J. Luchs***, Florida Vision Institute, West Palm Beach, FL, USA.

✉ Amy Zhuang-Yan
amy.zhuang-yan@springer.com

[1] Springer Nature, Private Bag 65901, Mairangi Bay, Auckland 0754, New Zealand

1 Introduction

Dry eye disease (DED) is a multifactorial ocular surface disorder characterized by a loss of homeostasis of the tear film, accompanied by ocular symptoms [1]. The severity of DED varies between patients and etiological factors include tear film instability and hyperosmolarity, inflammation, damage to the ocular surface, and neurosensory abnormalities [1, 2]. Individuals with DED can present with symptoms such as dryness, burning, stinging and blurred vision, alongside clinical signs such as reduced tear volume, ocular surface

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Perfluorohexyloctane ophthalmic solution: clinical considerations in DED
First eye drop approved in the USA that directly targets tear evaporation
Spreads quickly over the eye surface with minimal visual disturbance
Significantly improves the signs and symptoms of DED
Generally well tolerated

damage, and instability of the tear film [3]. The estimated prevalence of DED ranges from 5–50% worldwide and it is highly prevalent in females and adults of older age [4]. However, DED is also common in young adults and is linked to the use of digital devices [5, 6].

The etiology of DED can be classified as either aqueous-deficient, where lacrimal gland secretion of tears is reduced, or evaporative, where the rate of tear evaporation is excessive [1]. Both subtypes can exist as a continuum necessitating multiple treatment options that may be used simultaneously [1]. The outermost lipid layer of the tear film, formed by meibum secreted by the meibomian glands, functions to stabilize the tear film and prevent tear evaporation [3]. In meibomian gland dysfunction (MGD), reduced meibum quantity and/or quality, often due to meibomian gland blockage, dropout or inflammation, disrupts the tear film's lipid layer, leading to an excessive evaporation of tears [3]. The resultant tear hyperosmolarity leads to ocular surface desiccation and damage, which triggers a series of ocular surface inflammatory events that contribute to and continue the vicious cycle of DED [1, 3]. The majority of DED cases are predominantly evaporative in nature and MGD has been identified as the primary cause [1].

The main goal in the management of DED is to restore the homeostasis of the ocular surface and break the vicious cycle of the disease, with a focus on long-term prevention of relapse into this cycle and the reappearance of symptoms [2]. The management of DED involves transitioning from general treatments (e.g. tear substitutes) to tailored therapies based on individual requirements, considering both disease etiology and severity, rather than following a rigid stepwise algorithm [2, 6]. The range of treatment options available for evaporative DED associated with MGD have aimed at increasing the quality and quantity of meibomian gland secretions (e.g. warm compresses, intense pulse light, thermal pulsation), reducing ocular surface inflammation (e.g. oral doxycycline, oral essential fatty acid supplementation), or replacing the tear film lipid layer (e.g. over-the-counter lipid-containing artificial tears) [3, 7]. Pharmacological options that are currently approved by the US Food and Drug Administration (FDA) for DED target inflammation or tear production and include ophthalmic solutions such as lifitegrast (lymphocyte function-associated antigen-1 inhibitor), loteprednol etabonate (short-term corticosteroid), cyclosporine (immunosuppressant), and a nasal spray formulation of varenicline (cholinergic agonist) [8]. However, these treatments do not directly target the pathophysiology of excessive tear evaporation, the key driver of DED.

Perfluorohexyloctane ophthalmic solution (Miebo®) is a single entity, water-, steroid- and preservative-free, first-in-class semifluorinated alkane that is approved in the USA for the treatment of the signs and symptoms of DED [9]. This review summarizes the pharmacological, therapeutic efficacy, and tolerability data relevant to the use of perfluorohexyloctane ophthalmic solution in the treatment of the signs and symptoms of DED.

2 Pharmacodynamic Properties of Perfluorohexyloctane Ophthalmic Solution

Perfluorohexyloctane is a non-aqueous, physically, chemically, and physiologically inert liquid and is practically immiscible with water [9, 10]. It is a semifluorinated alkane and has the molecular formula of $C_{14}H_{17}F_{13}$ [9]. The drug consists of two parts, a lipophobic fluorocarbon segment and a lipophilic hydrocarbon segment, and thus has amphiphilic properties [11]. The exact mechanism of action underlying the efficacy of perfluorohexyloctane ophthalmic solution in DED is unknown, but it is thought to result from the hydrocarbon segment of the drug interacting with the lipophilic part of the tear film, while the fluorocarbon segment points towards the air, thus forming a monolayer at the air-liquid interface of the tear film [9, 11–13]. This action stabilizes the lipid layer of the tear film and inhibits aqueous layer evaporation [12, 14, 15]. The agent has a long residence time in the meibomian glands, which suggests that the meibomian glands may act as a depot replenishing the solution on the ocular surface between blinks [3, 14]. It is hypothesized that perfluorohexyloctane may dissolve altered viscous meibum blocked within the meibomian glands in MGD [14, 16]. In addition, the high oxygen content found in the lattice of the solution may support corneal healing in DED [17, 18].

Perfluorohexyloctane ophthalmic solution has a low surface tension of 19.7 mN/m [19] and a refractive index similar to that of water [14]. These physical properties contribute to its small drop size, long ocular residence time and ability to rapidly distribute across the ocular surface with minimal visual disturbance [15, 20].

In vitro, a perfluorohexyloctane ophthalmic solution layer significantly ($p < 0.0001$) reduced the evaporation rate of saline by 81% at 25°C, while artificial tears did not inhibit evaporation [21]. In addition, a single 11 µL drop of perfluorohexyloctane ophthalmic solution was shown to inhibit the evaporation of saline by 28% at 35°C, whereas a 125 nm layer of human meibum inhibited the evaporation of saline by 8% [21]. In healthy rabbit eyes with normal tear film, perfluorohexyloctane ophthalmic solution significantly ($p < 0.05$) improved the lipid layer grade compared with saline from day 5 onwards in a 7-day study [19].

In healthy human eyes, instillation of perfluorohexyloctane ophthalmic solution led to a significant ($p = 0.001$) decrease in corneal surface temperature and a significant ($p = 0.004$) increase in blinking rate, with no accompanying conscious ocular surface sensations [22]. While tear volume showed a slight increase at 5 min after instillation, this change was not statistically significant. These findings suggest that the ocular cooling effect of this solution may increase the activity of corneal cold thermoreceptors, resulting in increased reflex lacrimation and blinking, which could potentially relieve dry eye discomfort and pain [22].

Moreover, perfluorohexyloctane ophthalmic solution demonstrated tear film stabilizing effects in humans [15, 16, 20]. In a randomized, controlled trial in 48 adults with mild to moderate DED, instillation of this solution four times daily in both eyes for 4 weeks increased tear film thickness and lipid layer thickness over time compared with saline [15]. At week 4, tear film thickness increased significantly more in the active group than in the saline group [least-squares mean (LSM) difference 6.42%; $p = 0.01$]. Similar improvements were seen from baseline in lipid layer thickness (LSM difference 16.34%; $p < 0.01$) [15]. Furthermore, two prospective, observational, multicenter studies showed that treatment with perfluorohexyloctane ophthalmic solution for 6–8 weeks increased tear film break-up time and reduced ocular surface disease index scores in adults with mild to moderate DED due to hyper-evaporative [20] or MGD [16] etiologies.

3 Pharmacokinetic Properties of Perfluorohexyloctane Ophthalmic Solution

The pharmacokinetics of perfluorohexyloctane following topical ocular instillation in humans have not been quantitatively characterized [9]. However, the concentration of perfluorohexyloctane in blood following topical ocular administration in adults with DED was low [12]. Consistent with these data, following a single topical ocular administration of radiolabeled perfluorohexyloctane in rabbits, the concentration of radioactivity detected in blood and plasma was low, indicating that systemic absorption of perfluorohexyloctane is minimal [14]. In addition, while the majority of radiolabeled perfluorohexyloctane was found in the anterior ocular tissues, systemically, radioactivity was detected primarily in the gastrointestinal tract, suggesting that drug elimination is in part via fecal excretion [14]. In vitro, perfluorohexyloctane was not metabolized by human liver microsomes [9].

In healthy human eyes ($n = 5$), infrared emissivity images showed that perfluorohexyloctane ophthalmic solution was present on the ocular surface for at least 5 h following application of a single drop to the eye [23]. In addition, the highest average emissivity intensity of perfluorohexyloctane was seen in the upper region of the eye [23]. In rabbits, radiolabeled perfluorohexyloctane was primarily distributed in the anterior ocular tissues of the eye, with highest concentrations found in tears (for a minimum of 4 h) and meibomian glands (at least 8 h) [14].

4 Therapeutic Efficacy of Perfluorohexyloctane Ophthalmic Solution

In a randomized, double-masked, phase II trial (SEECASE), perfluorohexyloctane ophthalmic solution administered twice daily or four times daily significantly reduced ocular surface damage, as assessed by total corneal fluorescein staining (tCFS) in adults with MGD-associated DED compared with isotonic (0.9%) saline [12]. A four times daily regimen consistently exhibited a greater reduction in tCFS score than a twice daily regimen [12]. The efficacy of this regimen was subsequently assessed in adults with MGD-associated DED in two nearly identical randomized, double-masked, phase III trials, GOBI [24] and MOJAVE [25], both controlled with hypotonic saline (0.6%). This section focuses on data from GOBI and MOJAVE, as well as the long-term extension study (LTE) of GOBI, known as KALAHARI [26].

GOBI and MOJAVE included adults aged ≥18 years, with a self-reported history of DED in both eyes for ≥ 6 months, who met all of the following criteria in ≥ 1 eye (the same eye): tear film break-up time ≤ 5 s; unanesthetized Schirmer's tear test I ≥ 5 mm; total MGD score ≥ 3 (total score range 0–15); tCFS score ≥ 4 and ≤ 11 (according to the National Eye Institute scale); and ocular surface disease index score ≥25 [24, 25]. If both eyes qualified, the eye with the worse (higher) tCFS score at baseline was selected as the study eye. Exclusion criteria included: a history of ocular surgery or any procedure affecting the meibomian glands within the previous 6 months, DED

treatment, or topical glaucoma medication within the previous 60 days [24, 25]. Adults with a best-corrected visual acuity (BCVA) of 0.7 logarithm of the minimum angle resolution or worse in both eyes were also excluded [24]. Beginning 1 day before baseline and throughout the treatment period, patients were prohibited from wearing contact lenses or using other dry eye treatments, including artificial tears [24, 25]. Concurrent use of physical therapies, systemic antibiotics, and oral supplements for ocular conditions was allowed if doses had been stable for the past 30 days [24, 25].

After being stratified according to clinical site and by the patient's baseline visual analog scale (VAS) eye dryness score (< 70 vs ≥ 70), eligible recipients were randomized to self-administer one drop of perfluorohexyloctane ophthalmic solution or hypotonic saline solution (sodium chloride 0.6%, preserved with benzalkonium chloride 0.01%) into each eye four times daily for 8 weeks [24, 25].

Efficacy assessments included signs [tCFS and central corneal fluorescein staining (cCFS) scores] and symptoms (VAS scores) of DED (Table 1) [24, 25]. The two primary efficacy endpoints in both GOBI and MOJAVE were the change from baseline at week 8 in tCFS score and VAS eye dryness score, tested in an hierarchical order with tCFS first. If both primary efficacy endpoints were met, four key secondary efficacy endpoints were tested in the following hierarchical order: VAS dryness score at week 2, tCFS score at week 2, VAS burning/stinging score at week 8, and cCFS score at week 8. The efficacy analyses were conducted on the full analysis set, which included all adults who underwent randomization and received study medication, with no attribution of missing data [24, 25].

Baseline demographics and disease characteristics were generally similar across treatment groups in both trials [24, 25]. Other than DED associated with MGD, cataracts and vitreous detachment were among the common (≥ 10% of patients) occurrences in ocular medical history. Across GOBI and MOJAVE, the mean age of adults ranged from 53.3 to 61.6 years; the majority were female (72–80%) and white (69–83%); and the mean tCFS score, VAS dryness score and VAS burning/stinging score at baseline ranged from 6.7–7.1, 64.3–66.8 and 48.4–53.0, respectively [24, 25].

In both GOBI and MOJAVE, perfluorohexyloctane ophthalmic solution demonstrated clinically meaningful improvements in the signs and symptoms of DED versus saline [24, 25]. At week 8, the perfluorohexyloctane ophthalmic solution group showed a significantly ($p \leq 0.001$) greater mean reduction from baseline in both tCFS score and VAS eye dryness

Table 1 Efficacy of perfluorohexyloctane ophthalmic solution in adults with dry eye disease associated with meibomian gland dysfunction in two randomized, double-masked, multicenter, phase III studies

Treatment (no. of pts)	Mean change from baseline					
	CFS score[a]			VAS score[b]		
	tCFS (at wk 2)	tCFS (at wk 8)[c]	cCFS (at wk 8)	Dryness (at wk 2)	Dryness (at wk 8)[c]	Burning/stinging (at wk 8)
GOBI [24]						
PFHO (303)	− 1.7	− 2.0	− 0.4	− 18.0	− 27.4	− 23.6
SAL (294)	− 1.1	− 1.0	− 0.1	− 13.4	− 19.7	− 18.0
LSM BGD (95% CI)	− 0.6 (− 0.9 to − 0.2)**	− 0.97 (− 1.40 to − 0.55)**	− 0.2 (− 0.4 to − 0.1)**	− 4.7 (− 8.2 to − 1.2)*	− 7.6 (− 11.8 to − 3.4)**	− 5.5 (− 9.5 to − 1.6)*
MOJAVE [25]						
PFHO (311)	− 1.9	− 2.3	− 0.4	− 18.5	− 29.5	− 22.1
SAL (309)	− 1.3	− 1.1	− 0.1	− 10.5	− 19.0	− 13.7
LSM BGD (95% CI)	− 0.6 (− 1.0 to −0.2)**	− 1.2 (− 1.7 to − 0.8)**	− 0.3 (− 0.5 to − 0.2)**	− 7.8 (− 11.3 to − 4.3)**	− 10.2 (− 14.4 to − 6.1)**	− 7.3 (− 11.3 to − 3.4)**

BGD between-group difference, *cCFS* central CFS, *CFS* corneal fluorescein staining, *LSM* least-squares mean, *PFHO* perfluorohexyloctane ophthalmic solution qid, *pts* patients, *qid* four times daily, *SAL* hypotonic saline (0.6%) qid, *tCFS* total CFS, *VAS* visual analog scale, *wk* week

*$p < 0.01$, **$p \leq 0.001$ vs SAL

[a]Fluorescein staining of five areas of the cornea (inferior, superior, central, nasal, and temporal) rated by the investigator using the National Eye Institute scale from grade 0 (no staining) to grade 3 (heavy staining); tCFS score was the sum of the individual scores (maximum of 15)

[b]Rated by pts, considering both eyes together, on a scale ranging from 0 (no discomfort) to 100 (maximal discomfort)

[c]Primary endpoint

score, thereby meeting both primary efficacy endpoints (Table 1) [24, 25].

In addition, perfluorohexyloctane ophthalmic solution showed statistically significant improvements in all key secondary efficacy endpoints over saline (Table 1). Significant between-group differences in tCFS score and VAS dryness score were seen as early as week 2 [24, 25]. At week 8, perfluorohexyloctane ophthalmic solution recipients also showed significant improvements in cCFS score and VAS burning/stinging score when compared with saline recipients (Table 1).

At week 8, significantly ($p < 0.010$) more perfluorohexyloctane ophthalmic solution than saline recipients achieved a ≥3 step improvement in tCFS score (41.2% vs 27.2% of patients in GOBI [24]; 50% vs 30.7% in MOJAVE [25]) and a ≥30% reduction in VAS dryness score (57.4% vs 46.6% [24]; 65.6% vs 45.3% [25]).

A total of 208 patients from the GOBI trial were enrolled in KALAHARI and all received open-label perfluorohexyloctane ophthalmic solution (one drop in each eye four times daily) for 52 weeks [26]. In KALAHARI, those who continued perfluorohexyloctane ophthalmic solution treatment ($n = 97$) maintained their benefits from GOBI throughout the LTE. In patients who switched from saline ($n = 111$) benefits were seen by week 4 and were maintained for the rest of the LTE. The mean change from GOBI baseline in tCFS score and VAS dryness score in all patients at week 52 was − 2.1 and − 33.7, respectively [26].

Consistent with the benefits seen in efficacy endpoints, the proportion of tCFS responders and eye dryness responders at week 52 in the group who continued perfluorohexyloctane ophthalmic solution (38.1% and 52.6% of recipients, respectively) were similar to those in the group who switched from saline (32.4% and 49.5% of recipients, respectively) [26]. Furthermore, patients in KALAHARI reported satisfaction with perfluorohexyloctane ophthalmic solution use, as indicated by high VAS scores (ranging from 0 to 10) rated for instillation comfort (mean VAS score at week 52, 8.4) and ease of use (8.9) [26].

5 Tolerability of Perfluorohexyloctane Ophthalmic Solution

Perfluorohexyloctane ophthalmic solution was generally well tolerated in adults with DED associated with MGD, as seen in GOBI and MOJAVE (Sect. 4). In MOJAVE, no recipients discontinued treatment because of ocular adverse events (AEs) [25]. In GOBI, ocular AEs led to treatment discontinuation in one perfluorohexyloctane ophthalmic solution recipient (eye irritation) and in three saline recipients (conjunctivitis, dry eye, and punctate keratitis) [24]. In GOBI, ocular AEs that were considered as drug-related were numerically more frequent in the perfluorohexyloctane ophthalmic solution group than in the saline group (6.3% vs 3.1%) [24], although such a pattern was not seen in MOJAVE (6.4% vs 6.8%) [25]. In both trials, most ocular AEs were mild or moderate in severity and no serious ocular AEs occurred [24, 25]. The most common adverse reaction to perfluorohexyloctane ophthalmic solution was blurred vision; blurred vision and conjunctival redness were reported in 1–3% of recipients [9]. In GOBI, blurred vision was reported to be transient in nature and typically resolved within minutes of onset [24].

In a pooled analysis of GOBI and MOJAVE, ocular AEs in the study eye occurred in 9.0% of perfluorohexyloctane ophthalmic solution recipients ($n = 614$) and 7.5% of saline recipients ($n = 603$) [27]. The most common ocular AEs are shown in Fig. 1. Ocular AEs that occurred more frequently (difference ≥0.5% of patients) in the perfluorohexyloctane ophthalmic solution group than in the saline group were blurred vision and blepharitis (Fig. 1) [27].

In both trials, perfluorohexyloctane ophthalmic solution was not associated with any clinically meaningful changes in BCVA, slit-lamp examination, intraocular pressure (IOP), or dilated fundoscopy examination [24, 25]. Non-ocular AEs reported in the perfluorohexyloctane ophthalmic solution and saline groups (9.6% vs 7.5% of patients in GOBI; 7.1% vs 5.2% in MOJAVE) were not considered to be related to study treatment and none of them led to treatment discontinuation [24, 25].

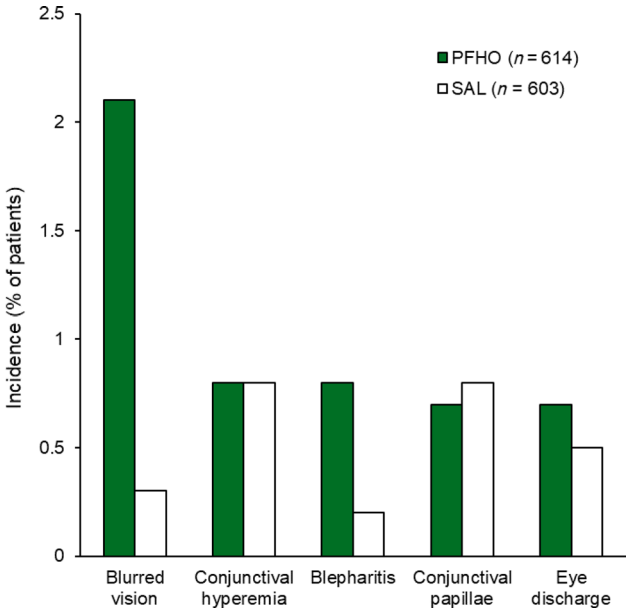

Fig. 1 Most common ocular adverse events (> 0.5% of patients in either treatment group) in the pooled analysis of the randomized, double-masked, multicenter, phase III GOBI and MOJAVE studies in adults with dry eye disease associated with meibomian gland dysfunction [27]. *PFHO* perfluorohexyloctane ophthalmic solution, *SAL* hypotonic saline (0.6%)

The tolerability profile of perfluorohexyloctane ophthalmic solution during the open-label LTE was consistent with that seen in the GOBI and MOJAVE trials [26]. In KALAHARI, ocular AEs led to treatment discontinuation in five perfluorohexyloctane ophthalmic solution recipients (one case each of blurred vision, chalazion, dry eye, increased lacrimation, and increased IOP). Of these AEs, blurred vision, chalazion, and increased lacrimation were considered by the investigator as treatment-related, and all were reported resolved except for chalazion. Overall, 13.9% of perfluorohexyloctane ophthalmic solution recipients reported ≥ 1 ocular AE in either eye, with 6.3% of ocular AEs considered to be treatment-related. Most ocular AEs were mild or moderate in severity and no serious ocular AEs occurred. The most common (≥ 1% of patients) ocular AEs were vitreous detachment (1.9%, none were considered treatment-related), allergic conjunctivitis (1.4%), blurred vision (1.4%), and increased lacrimation (1.4%). Clinically meaningful findings in BCVA, IOP, slit-lamp biomicroscopy, or dilated fundoscopy were few and none were identified as a safety concern with the long-term use of perfluorohexyloctane ophthalmic solution [26].

6 Dosage and Administration of Perfluorohexyloctane Ophthalmic Solution

Perfluorohexyloctane ophthalmic solution is approved in the USA for the treatment of the signs and symptoms of DED [9]. It comes in a 3 mL multi-dose bottle containing 100% perfluorohexyloctane (1.338 g/mL). The recommended dosage is one drop instilled into each eye four times daily. Contact lenses should be removed prior to instillation and may be reinserted 30 min following administration [9]. Local prescribing information should be consulted for further information.

7 Current Status of Perfluorohexyloctane Ophthalmic Solution in the Management of Dry Eye Disease

The standard of care for the management of DED involves taking into consideration the disease severity and etiology in each individual and may require the use of several treatment options to address multiple aspects of DED (Sect. 1). Although various pharmacological ophthalmic treatment options (e.g. lifitegrast, cyclosporine, loteprednol etabonate) and nasal spray (varenicline) are US FDA-approved for use in DED (Sect. 1), perfluorohexyloctane ophthalmic solution is currently the only prescription eye drop approved in the USA that directly targets excessive tear evaporation, the key driver of DED. It is worth noting that perfluorohexyloctane ophthalmic solution has unique physical properties that are advantageous over other topical ophthalmic solutions, including its small drop size and ability to spread quickly with minimal visual disturbance (Sect. 2). The non-aqueous nature of perfluorohexyloctane allows it to be preservative-free and thus avoids any ocular toxicity associated with exposure to preservatives that are typically used in multidose ophthalmic formulations [2].

Approval of perfluorohexyloctane ophthalmic solution for the treatment of the signs and symptoms of DED was based on data from the phase III GOBI and MOJAVE trials in adults with DED associated with MGD (Sect. 4). During the 8-week study period, treatment with perfluorohexyloctane ophthalmic solution instilled four times daily was associated with statistically significant and clinically meaningful improvements in the signs and symptoms of DED relative to hypotonic saline [24, 25]. The efficacy was evident within 2 weeks and, based on data from KALAHARI, is sustained for up to 52 weeks with ongoing treatment. Perfluorohexyloctane ophthalmic solution was generally well tolerated for up to 52 weeks, with mostly mild or moderate ocular AEs and low treatment discontinuation rates (Sect. 5). Blurred vision was the most common ocular AE of the solution; however, it was reported to be transient in nature and resolved within minutes of onset.

The findings of GOBI and MOJAVE have limitations, including the exclusion of individuals with severe dry eye (tCFS score >11), the potential treatment unmasking due to differences in drop size, and the confounding presence of benzalkonium chloride in the hypotonic saline-control group. Hypotonic saline was used as the control because a vehicle control was not feasible due to perfluorohexyloctane ophthalmic solution being a 100% active single entity. However, this choice represents a potential strength because hypotonic solutions are known to exert a therapeutic effect in DED, thereby enhancing the rigor of the comparative outcomes. One open-label study (n = 30) found a trend that perfluorohexyloctane ophthalmic solution was more effective than two aqueous-based lipid-containing eye drops, but the differences between treatment groups in non-invasive break-up time were not statistically significant [28]. Real-world studies designed to confirm the effectiveness of perfluorohexyloctane ophthalmic solution for the treatment of DED in clinical practice would be of value.

In conclusion, perfluorohexyloctane ophthalmic solution is effective and generally well tolerated in adults with DED associated with MGD. As the first and currently the only US FDA-approved prescription treatment directly addressing the pathophysiology of excessive tear evaporation,

perfluorohexyloctane ophthalmic solution is a valuable emerging option for the management of DED.

Data Selection Perfluorohexyloctane: 119 records identified	
Duplicates removed	2
Excluded during initial screening (e.g. press releases; news reports; not relevant drug/indication; preclinical study; reviews; case reports; not randomized trial)	50
Excluded during writing (e.g. reviews; duplicate data; small patient number; nonrandomized/phase I/II trials)	39
Cited efficacy/tolerability articles	5
Cited articles not efficacy/tolerability	23
Search Strategy: EMBASE, MEDLINE and PubMed from 1946 to present. Clinical trial registries/databases and websites were also searched for relevant data. Key words were perfluorohexyloctane ophthalmic solution, MIEBO, NOV03 and dry eye disease. Records were limited to those in the English language. Searches last updated 27 Feb 2024	

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Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability Not applicable.

References

1. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II definition and classification report. Ocul Surf. 2017;15(3):276–83.
2. Jones L, Downie LE, Korb D, et al. TFOS DEWS II management and therapy report. Ocul Surf. 2017;15(3):575–628.
3. Sheppard JD, Nichols KK. Dry eye disease associated with meibomian gland dysfunction: focus on tear film characteristics and the therapeutic landscape. Ophthalmol Ther. 2023;12(3):1397–418.
4. Stapleton F, Alves M, Bunya VY, et al. TFOS DEWS II epidemiology report. Ocul Surf. 2017;15(3):334–65.
5. Wrobel-Dudzinska D, Osial N, Stepien PW, et al. Prevalence of dry eye symptoms and associated risk factors among university students in Poland. Int J Environ Res Public Health. 2023;20(2):1313.
6. Barabino S, Benitez-Del-Castillo JM, Fuchsluger T, et al. Dry eye disease treatment: the role of tear substitutes, their future, and an updated classification. Eur Rev Med Pharmacol Sci. 2020;24(17):8642–52.
7. Sabeti S, Kheirkhah A, Yin J, et al. Management of meibomian gland dysfunction: a review. Surv Ophthalmol. 2020;65(2):205–17.
8. Mukamal R. Improved dry eye drugs for 2022 and beyond. 2021. https://www.aao.org/eye-health/tips-prevention/new-dry-eye-treatments-ocular-surface-disease. Accessed 27 Feb 2024.
9. US Food and Drug Administration. MIEBO (perfluorohexyloctane ophthalmic solution) for topical ophthalmic use: US prescribing information. 2024. https://dailymed.nlm.nih.gov/dailymed. Accessed 27 Feb 2024.
10. Agarwal P, Scherer D, Günther B, et al. Semifluorinated alkane based systems for enhanced corneal penetration of poorly soluble drugs. Int J Pharm. 2018;538(1–2):119–29.
11. Tsagogiorgas C, Otto M. Semifluorinated alkanes as new drug carriers-an overview of potential medical and clinical applications. Pharmaceutics. 2023;15(4):1211.
12. Tauber J, Wirta DL, Sall K, et al. A randomized clinical study (SEECASE) to assess efficacy, safety, and tolerability of NOV03 for treatment of dry eye disease. Cornea. 2021;40(9):1132–40.
13. Liu X, Riess J, Krafft M. Self-organization of semifluorinated alkanes and related compounds at interfaces: thin films, surface domains and two-dimensional spherulites. Bull Chem Soc Jpn. 2018;91(5):846–57.
14. Krösser S, Spencer E, Grillenberger R, et al. Ocular and systemic distribution of ^{14}C- perfluorohexyloctane following topical ocular administration to rabbits [abstract no. 2656 plus poster]. Invest Ophthalmol Vis Sci. 2018;59(9):2656.
15. Schmidl D, Bata AM, Szegedi S, et al. Influence of perfluorohexyloctane eye drops on tear film thickness in patients with mild to moderate dry eye disease: a randomized controlled clinical trial. J Ocul Pharmacol Ther. 2020;36(3):154–61.
16. Steven P, Augustin AJ, Geerling G, et al. Semifluorinated alkane eye drops for treatment of dry eye disease due to meibomian gland disease. J Ocul Pharmacol Ther. 2017;33(9):678–85.
17. Borchman D, Vittitow J, Kissling R, et al. Spectroscopic characterization of perfluorohexyloctane, an eye drop for dry eye disease [abstract no. 3975-B0292 plus poster]. Invest Ophthalmol Vis Sci. 2023;64(8):3975.
18. Stolowich N, Vittitow J, Kissling R, et al. Oxygen-carrying capacity of perfluorohexyloctane, a novel eye drop for dry eye disease. Curr Ther Res Clin Exp. 2023;98(100705):1–5.
19. Agarwal P, Khun D, Krösser S, et al. Preclinical studies evaluating the effect of semifluorinated alkanes on ocular surface and tear fluid dynamics. Ocul Surf. 2019;17(2):241–9.
20. Steven P, Scherer D, Krösser S, et al. Semifluorinated alkane eye drops for treatment of dry eye disease-a prospective, multicenter noninterventional study. J Ocul Pharmacol Ther. 2015;31(8):498–503.
21. Vittitow J, Kissling R, DeCory H, et al. In vitro inhibition of evaporation with perfluorohexyloctane, an eye drop for dry eye disease. Curr Ther Res Clin Exp. 2023;98(100704):1–7.
22. Delicado-Miralles M, Velasco E, Díaz-Tahoces A, et al. Deciphering the action of perfluorohexyloctane eye drops to reduce ocular discomfort and pain. Front Med (Lausanne). 2021. https://doi.org/10.3389/fmed.2021.709712.
23. Borchman D, Cavet M, DeCory H, et al. Visualization of perfluorohexyloctane, an eye drop for dry eye disease, on the human

ocular surface using infrared emissivity [poster]. Annual meeting of the American Academy of Ophthalmology. 2023.
24. Tauber J, Berdy GJ, Wirta DL, et al. NOV03 for dry eye disease associated with meibomian gland dysfunction: results of the randomized phase 3 GOBI study. Ophthalmology. 2023;130(5):516–24.
25. Sheppard JD, Kurata F, Epitropoulos AT, et al. NOV03 for signs and symptoms of dry eye disease associated with meibomian gland dysfunction: the randomized phase 3 MOJAVE study. Am J Ophthalmol. 2023;252:265–74.
26. Protzko EE, Segal BA, Korenfeld MS, et al. Long-term safety and efficacy of perfluorohexyloctane ophthalmic solution for the treatment of patients with dry eye disease: the KALAHARI Study. Cornea. 2023. https://doi.org/10.1097/ICO.0000000000003418.
27. Fahmy A, Evans D, Harthan J, et al. Perfluorohexyloctane (NOV03) for dry eye disease associated with meibomian gland dysfunction: pooled analysis of GOBI and MOJAVE studies [poster]. Annual Meeting of the American Optometric Association. 2023.
28. Groß D, Kaercher T. Comparison of the clinical efficacy of three different eye drops for the treatment of dry eye. EC Ophthalmol. 2021;12(6):32–44.

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