Perfluorohexyloctane (MIEBO) Ophthalmic Solution
National Drug Monograph
December 2023
VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action
Dry eye disease (DED) can be classified as aqueous-deficient, due to reduced lacrimal secretion and evaporative DED, which results from excessive evaporation of the tear film, or a combination of the two. Meibomian gland dysfunction (MGD) is the primary cause of evaporative DED. Meibomian glands secrete lipids (meibum) needed to form the outermost layer of the tear film. In MGD, reduced meibum secretion and or changes in meibum composition, affect the lipid layer of the tear film leading to tear film instability and increased evaporative water loss. This in turn increases the osmolarity of the tear and can result in inflammation and apoptosis of ocular surface cells.

Although the exact mechanism of action is not known currently, perfluorohexyloctane is thought to form an anti-evaporative barrier over the ocular surface, thereby reducing evaporation of the aqueous component of the tear film.

Indication(s) Under Review in This Document
Treatment of the signs and symptoms of dry eye disease

Dosage Form(s) Under Review
- Perfluorohexyloctane 100% Ophthalmic solution (preservative free) available in 5mL bottle
- Administered as one drop in each eye four times daily

Clinical Evidence Summary

Efficacy Considerations
Two 8-week phase 3 trials (GOBI and MOJAVE) compared perfluorohexyloctane to hypotonic saline 0.6% in patients with DED and clinical symptoms of MGD. Hypotonic saline 0.6% can reduce hyperosmolarity of the tear film and can be effective in treating DED. Long-term safety and tolerability were evaluated in a 12 month open-label extension study (KALAHARI) in patients who completed the GOBI trial without protocol violation. All patients received perfluorohexyloctane in KALAHARI.

Study drug was administered four times daily. Use of contact lenses, artificial tears, and other DED treatments were prohibited. Lid scrubs, lid wipes, warm compresses, systemic antibiotics (e.g., tetracyclines), and oral supplements for treatment of ocular conditions were permitted, if stable within the 30 days before baseline and were continued throughout the trial. In KALAHARI, artificial tears were allowed after week 4.

The primary sign and symptom outcomes were change from baseline in total corneal fluorescein staining (tCFS) and eye dryness score (EDS) at week 8. Fluorescein staining of 5 areas of the cornea (inferior, superior, central, nasal, and temporal) was rated by the investigator using the National Eye Institute scale from grade 0 (no staining) to grade 3 (heavy staining); the tCFS score was the sum of the individual scores (maximum of 15). The EDS is a validated

assessment tool where patients rate their dry eye symptoms using a visual analogue scale (0=no discomfort, 100=maximal discomfort). Values equal to or greater than 60 indicate moderate to severe disease.

Key inclusions: ≥18 years of age, self-reported history of DED in both eyes for ≥ 6 months

- Tear film break-up time (TFBUT) ≤ 5 seconds (> 8-10 seconds is usually considered normal)
- Ocular surface disease index (OSDI) score ≥ 25 (total score ranges 0-100; score 23 to 32 represents moderate disease and a score over 33 as severe dry eye)
- Unanesthetized Schirmer I test ≥5 mm at 5 minutes (evaluates aqueous tear production from lacrimal glands; more than 10mm is considered normal)
- Total Meibomian Gland Disease (MGD) score ≥ 3 (5 central glands on lower eyelid were evaluated, each was scored from 0 to 3; 0 = normal; 1 = thick/ yellow, whitish, particulate; 2 = paste; and 3 = none/occluded; the total MGD score ranged from 0 to 15)
- tCFS score 4 to 11 according to the National Eye Institute scale (total range for tCFS score is 0-15; severe dry eye is tCFS score >11).

Key exclusions: clinically significant slit-lamp findings, active blepharitis; active ocular allergies; ocular or systemic infection; history of herpetic keratitis; intraocular surgery or ocular laser surgery within the previous 6 months; procedures affecting the meibomian glands within the previous 6 month (e.g., Lipiflow, intense pulse light); use of contact lenses within the previous month; use of topical steroids, topical cyclosporine, lifitegrast, serum tears, or topical glaucoma medication within the previous 60 days.

Demographics: Mean age 57 years (39% >/= 65 years); 34% male; 75% White

Perfluorohexyloctane significantly improved tCFS and EDS compared to saline 0.6%. Improvement was noted at week 2 at the first assessment period. More patients receiving perfluorohexyloctane had a 3-step or more improvement in tCFS per the NEI scale and a 30% or greater improvement in the EDS VAS score than those in the saline group. Effects appear to be maintained over a 12 month period. (**Table 1**).

A similarly designed study conducted in Chinese patients showed significant treatment difference in tCFS and EDS scores. This study also evaluated and found a significant improvement in OSDI score. There was no significant improvement versus saline 0.6% for MGD score, Schirmer I test, and TFBUT.

Table 1: Efficacy Results at Week 8 from Phase 3 Clinical Trials

Study	Treatments	Baseline	tCFS	EDS (VAS)	Eye burning /stinging score (VAS)	Improv in tCFS >/= 3 steps on NEI scale (%pts)	>/= 30% ↓ in EDS VAS score (%pts)
GOBI 56 days	PFHO (n=303) Saline 0.6% (n=294) Use of artificial tears was prohibited	• tCFS score 6.7 • EDS VAS score 67 • Eye burning/ stinging VAS score 53 • MGD score 7.6 • TFBUT 3.2 sec • OSDI score 54 • Schirmer's test (unanesthetized) 11.9mm	-2.0* -1.0	-27.4* -19.7	-23.6* -18.0	41.2* 27.2	57.4 46.6
MOJAVE 56 days	PFHO (n=311) Saline 0.6% (n=309)	• tCFS score 7.0 • EDS VAS score 65 • Eye burning/	-2.3* -1.1	-29.5* -19.0	-22.1* -13.7	50.0* 30.7	65.6* 45.3

	Use of artificial tears was prohibited	stinging VAS score 49 • Total MGD score 8.0 • TFBUT 3.2 sec • OSDI score 56 • Schirmer's test (unanesthetized) 12.8mm					
KALAHARI (GOBI extension) 52 weeks	PFHO (n=208)** Use of artificial tears was allowed after week 4	• tCFS score 6.6 • EDS VAS score 68 • Eye burning/ stinging VAS score 53 • MGD score 7.1 • TFBUT 3.2 sec • OSDI score 55 • Schirmer's test (unanesthetized) 12mm	-2.1	-34	-30	38 (PFHO→PFHO) 32 (saline→PFHO)	53 (PFHO→PFHO) 50 (saline→PFHO)

Abbreviations: EDS=Eye dryness score (0-100 visual analog scale; 0=no discomfort, 100=maximal discomfort); MGD=meibomian gland dysfunction; National Eye Institute (NEI); OSDI=ocular surface disease index; PFHO=perfluorohexyloctane; tCFS=Total corneal fluorescein staining; TFBUT=tear film break-up time; VAS=visual analog scale

*Statistically significant vs saline 0.6%

**208 patients from GOBI (PFHO n=97 and n=111 saline) were rolled over into KALAHARI. All patients in KALAHARI received open-label PFHO

Safety Considerations

- **Boxed warnings:** None
- **Contraindications:** None
- **Other warnings/precautions**: None
- **Adverse reactions**
  - **Common:** Most common ocular adverse reaction was blurred vision reported in less than 4% of individuals.
  - **Serious Adverse events:** None
  - **Deaths:** None reported in GOBI and MOJAVE. 1 death in KALAHARI unrelated to study drug
  - **Discontinuation due to adverse events:** GOBI (0.3% and 1% PFHO and saline respectively); MOJAVE (none); KALAHARI (3.1% PFHO→PFHO and 1.8% saline→PFHO)- 2 were related to blurred vision, 1 chalazion, 1 dry eye, and 1 increased lacrimation

Other Considerations

- Perfluorohexyloctane should not be administered while wearing contact lenses. Advise patients that contact lenses should be removed prior to and for at least 30 minutes after administration of perfluorohexyloctane
- Perfluorohexyloctane was not evaluated with other topical medications in the pivotal clinical studies. Standard clinical practice is to wait 10-15 minutes between topical ophthalmic drops. It may be good practice to instill any aqueous drops first, followed by perfluorohexyloctane since perfluorohexyloctane is known to have a long ocular surface residence time. (Personal communication with Bausch & Lomb- does not constitute endorsement by Bausch & Lomb Americas, Inc.)

- The instructions for how to administer differs from standard eye drop bottles (see product labeling). There is a potential for administration errors.
- Patients may find difficulty with adhering to four times daily administration
- Concurrent use of perfluorohexyloctane with cyclosporine or lifitegrast has not been evaluated in DED
- In Clinicaltrials.gov, no trials were listed comparing perfluorohexyloctane to other agents used to treat dry eye disease such as cyclosporine or lifitegrast

Other Therapeutic Options

The management of MGD includes eyelid hygiene, warm eye compresses, and ophthalmic lubricants. Other treatments that are administered in the office setting include manual expression, thermal pulsation, intense pulsed light, and microblepharoexfoliation.

Drugs, excluding artificial tears and topical steroids, for treatment of DED are listed in table 3.

Table 2 Treatment Alternatives (excludes artificial tears and topical steroids)

Drug	Formulary Status	Clinical Guidance
Cyclosporine 0.05% emulsion	PA-F	• Immunomodulator • To Increase tear production in those with keratoconjunctivitis sicca (dry eye) • Can take 3-6 months to notice increase in tear production or symptom improvement • Most common AE: ocular burning 17%
Cyclosporine 0.09% solution	NF	• Immunomodulator • To Increase tear production in those with keratoconjunctivitis sicca (dry eye) • Most common AEs: instillation site pain 22%; hyperemia 6%
Lifitegrast solution	PA-F	• Immunomodulator • Treatment of signs and symptoms of dry eye disease • Symptom relief can begin as early as 2 weeks • Most common AEs: instillation site irritation 15.2%; instillation site reaction 12.3%; instillation site pain 9.8%; dysgeusia 14.5%
Varenicline nasal spray	NF w/CFU	• Cholinergic agonist • Treatment of signs and symptoms of dry eye disease • Meaningful increase in production of basal tear film as early as 4 weeks • Most common AEs: sneezing (82%) cough (16%); throat irritation (13%); instillation-site (nose) irritation (8%)

AE=adverse events; CFS=corneal fluorescein staining; CsA= cyclosporine A; CFU=criteria for use; EDS=eye dryness score; ICSS=inferior corneal staining score; NF=nonformulary; PA-F=prior authorization-formulary; STS=Schirmer's Test score; TD=treatment difference
**Trial results not intended for direct comparison as study design, patient population, treatment endpoints, etc. differed among trials

Projected Place in Therapy

Patients with dry eye disease due to MGD who have not responded to or tolerated treatment with artificial tears, topical cyclosporine, and lifitegrast.

REFERENCES

Perfluorohexyloctane ophthalmic solution (MIEBO) [prescribing Information online]. Bridgewater, NJ: Bausch & Lomb Americas Inc. LABEL (fda.gov)

Schmidl D, Bata AM, Szegedi S, Aranha Dos Santos V, et al. influence of perfluorohexyloctane eye drops on tear film thickness in patients with mild to moderate dry eye disease: a randomized controlled trial. J Ocul Pharmacol Ther. 2020 Apr;36(3):154-161. doi: 10.1089/jop.2019.0092. https://pubmed.ncbi.nlm.nih.gov/31895638/

Tauber J, Wirta DL, Sall K, Majmudar PA, Willen D, Krösser S; SEECASE study group. A Randomized Clinical Study (SEECASE) to Assess Efficacy, Safety, and Tolerability of NOV03 for Treatment of Dry Eye Disease. Cornea. 2021 Sep 1;40(9):1132-1140.

Tauber J, Berdy GJ, Wirta DL, Krösser S, Vittitow JL; GOBI Study Group.NOV03 for Dry Eye Disease Associated with Meibomian Gland Dysfunction: Results of the Randomized Phase 3 GOBI Study. Ophthalmology. 2023 May;130(5):516-524. doi: 10.1016/j.ophtha.2022.12.021.

Sheppard JD, Kurata F, Epitropoulos AT, Krösser S, Vittitow JL; MOJAVE Study Group.NOV03 for Signs and Symptoms of Dry Eye Disease Associated With Meibomian Gland Dysfunction: The Randomized Phase 3 MOJAVE Study. Am J Ophthalmol. 2023 Mar 21;252:265-274. doi: 10.1016/j.ajo.2023.03.008.

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 Nov 3. doi: 10.1097/ICO.0000000000003418. Online ahead of print.

Tian L, Gao Z, Zhu L, Shi X, et al. Perfluorohexyloctane Eye Drops for Dry Eye Disease Associated With Meibomian Gland Dysfunction in Chinese Patients: A Randomized Clinical Trial. JAMA Ophthalmol. 2023 Apr 1;141(4):385-392. doi: 10.1001/jamaophthalmol.2023.0270.

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