CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	NDA
Application Number	216675
PDUFA Goal Date	June 28, 2023
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Reviewer Name(s)	Carla Darling, Pharm.D., BCPS
Team Leader	Jacqueline Sheppard, Pharm.D.
Associate Director for REMS Design and Evaluation	Laura Zendel, Pharm.D., BCPS
Review Completion Date	May 18, 2023
Subject	Evaluation of Need for a REMS
Established Name	Perfluorohexyloctane
Trade Name	Meibo
Name of Applicant	Bausch & Lomb Incorporated
Therapeutic Class	Semifluorinated alkane
Formulation(s)	topical sterile ophthalmic solution
Dosing Regimen	Instill one drop four times daily into each eye

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Meibo (perfluorohexyloctane) is necessary to ensure the benefits outweigh its risks. Bausch & Lomb Incorporated (Applicant) submitted a New Drug Application (NDA) 216675 for perfluorohexyloctane with the proposed indication for the treatment of the signs and symptoms of dry eye disease (DED) associated with meibomian gland dysfunction (MGD). During the course of the review, it was determined that the efficacy data did not support limiting the approval of the indication to DED with MGD; therefore, the indication was revised to "perfluorohexyloctane is indicated for treatment of the signs and symptoms of dry eye disease."[1] The applicant did not submit a proposed REMS or risk management plan with this application.

DRM and the Division of Ophthalmology agree that a REMS is not necessary to ensure the benefits of perfluorohexyloctane outweigh its risks. The two pivotal, saline-controlled phase 3 trials demonstrated the benefit of perfluorohexyloctane for the treatment of DED with statistically significant improvements in a clinically relevant sign (total corneal fluorescein staining score based on the National Eye Institute scale) and symptom (visual analog scale dryness score) of DED compared to saline. The main risk associated with perfluorohexyloctane is blurred vision. This risk is included in the adverse reactions section of the label. Likely prescribers of perfluorohexyloctane should be familiar with monitoring and management of this risk. Based on the safety and efficacy demonstrated in clinical trials, the benefit-risk profile is acceptable and risk mitigation beyond labeling is not required.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Meibo (perfluorohexyloctane) is necessary to ensure the benefits outweigh its risks. Bausch & Lomb Incorporated (Applicant) submitted New Drug Application (NDA) 216675 for perfluorohexyloctane with the proposed indication for the treatment of the signs and symptoms of dry eye disease (DED) associated with meibomian gland dysfunction (MGD). This application is under review in the Division of Ophthalmology. The applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Perfluorohexyloctane, a new molecular entity (NME),[a] is a semifluorinated alkane proposed for treatment of DED associated with MGD. The specific mechanism of action in DED is unknown. However, the Applicant proposes that due to its low surface tension, perfluorohexyloctane rapidly spreads across the ocular surface, interacts with the lipophilic part of the tear film, and forms a monolayer at the air-

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

liquid interface of the tear film which stabilizes the natural tear film and reduces evaporation. Perfluorohexyloctane ophthalmic solution is intended for long-term use.[2, b] The proposed dosage regimen is to instill one drop into each eye four times daily. Perfluorohexyloctane is intended for administration by patients or caregivers in the outpatient setting.

Perfluorohexyloctane was approved in Europe and subsequently registered in New Zealand and Australia. If approved, perfluorohexyloctane will be the first drug in the pharmacological class of semifluorinated alkane in the United States.

2.2. Regulatory History

The following is a summary of the regulatory history for NDA 216675 relevant to this review:

- 06/28/2022: NDA 216675 submission for the treatment of DED associated with MGD received
- 01/11/2023: A mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no major safety issues identified for perfluorohexyloctane.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

DED is a disorder characterized by reduced film production or tear film instability which results in symptoms of discomfort, visual disturbance, and inflammatory disease of the ocular surface.[3] DED can be due to dysfunction of one or more ocular structures that create and regulate the tear film components, including the lacrimal glands, meibomian glands, cornea, and conjunctiva.[3,4] Meibomian gland dysfunction (MGD) is a major cause of evaporative dry eye.[3,5] Patients with mild and moderate DED may have symptoms of irritation, itching, soreness, ocular discomfort, burning, or intermittent blurred vision while patients with severe DED have an increasing frequency of visual symptoms that may become constant as well as potentially disabling.[3] Reversible conjunctival squamous metaplasia and punctate epithelial erosions of the conjunctiva and cornea can develop in many patients who have clinically significant dry eye. In cases of severe dry eye with underlying inflammatory systemic conditions, ocular surface keratinization, corneal scarring, thinning, or neovascularization, microbial or sterile corneal ulceration with possible perforation, and severe visual loss may occur.[3c]

In a recent systematic review and meta-analysis, the prevalence of dry eye ranges from 5.3% to 14.5%, and the prevalence of MGD ranges from 10.4% to 55.4% in the United States (U.S.) population.[6, d]

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[c] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

[d] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

3.2. Description of Current Treatment Options

Current treatment goals for DED are to reduce or alleviate signs and symptoms of dry eye, maintain or improve visual function, and reduce or prevent ocular surface damage.[3] Food and Drug Administration (FDA) approved treatments for dry eyes include products to increase tear production or to treat signs and symptoms of dry eye disease. None of these treatments provide a permanent cure and none have been systematically evaluated in patients with MGD. Development of additional therapeutic options continues to be important to address the underlying disease process of DED.

Available FDA approved drugs for the treatment of DED include those intended to increase tear production such as topical cyclosporine (e.g., Restasis and Cequa) as well as those intended to treat signs and symptoms of DED such as topical lifitegrast, topical loteprednol etabonate, and intranasal varenicline. See Table 1 in Appendix 10.2 for a list of current FDA approved treatments. Nonpharmacological treatment options for MGD include warm compresses, physical heating and expression of the meibomian glands, and intense pulse light treatment.[3,5]

4. Benefit Assessment

The efficacy and safety of perfluorohexyloctane for the treatment of the signs and symptoms of DED associated with MGD is supported by two phase 3, pivotal trials, study NVU-003 (NCT04139798) and study BL-904 (NCT04567329). Both studies were multicentered, randomized, double-blinded, placebo-controlled to evaluate the efficacy and safety of perfluorohexyloctane in adults with DED. A total of 1,217 patients (Study NVU-003 and Study BL-904) were randomized 1:1 to receive at least one drop of perfluorohexyloctane ophthalmic solution (n = 614) or saline (0.6% sodium chloride solution preserved with benzalkonium chloride) ophthalmic solution (n = 603), bilaterally, four times a day (QID) for 8 weeks. There were two primary efficacy endpoints of the studies using hierarchical fixed sequence testing to maintain an overall 2-sided alpha = 0.05 level. The first primary endpoint was the difference in the mean change from baseline to day 57 in total corneal fluorescein staining (tCFS) score based on the National Eye Institute (NEI) scale. The second primary end point was change from baseline to day 57 in the visual analog scale (VAS) dryness score. The tCFS is a measure of sign associated with DED, whereas the VAS dryness score is a measure of a symptom. Secondary efficacy endpoints included:

- Change from baseline of VAS dryness score at Day 15.
- Change from baseline in tCFS (NEI scale) score at Day 15.
- Change from baseline of VAS burning/stinging at Day 57.
- Change from baseline in central corneal fluorescein staining (cCFS) (NEI scale) at Day 57.

The review team determined that the primary efficacy data to support approval of perfluorohexyloctane was demonstrated in the two pivotal studies, study NVU-003 and study BL-904. Perfluorohexyloctane showed statistically significant improvement compared to the control in both an objective sign and a subjective symptom of DED. Table 2 highlights the results of the co-primary endpoints for both studies. In addition, all 4 secondary endpoints showed a statistically significant differences between the perfluorohexyloctane and saline groups in both studies.

Table 2: Results of the Primary Efficacy Endpoints*

	Study NVU-003		Study BL-904	
Change from Baseline	**NOV03** (n=303)	**Saline** (n=294)	**NOV03** (n=311)	**Saline** (n=309)
tCFS (Study Eye)				
N	289	279	302	296
Mean (SD)	-2.0 (2.6)	-1.0 (2.7)	-2.3 (2.8)	-1.1 (2.9)
Median (Min, Max)	-2.0 (-10, 7)	-1.0 (-9, 7)	-2.5 (-11, 7)	-1.0 (-11, 7)
LS mean	-2.22	-1.28	-2.80	-1.52
NOV03 – Saline (95% CI)	**-0.95 (-1.35, -0.54)**		**-1.28 (-1.69, -0.87)**	
p-value	**<0.0001**		**<0.0001**	
Dryness Score (VAS)				
N	289	279	302	296
Mean (SD)	-27.4 (27.9)	-19.7 (26.7)	-29.5 (28.6)	-19.0 (27.2)
Median (Min, Max)	-29.0 (-90, 50)	-18.0 (-96, 66)	-30.5 (-90, 53)	-18.5 (-100, 90)
LS mean	-27.75	-20.31	-29.54	-19.56
NOV03 – Saline (95% CI)	**-7.44 (-11.74, -3.13)**		**-9.98 (-14.25, -5.72)**	
p-value	**0.0007**		**<0.0001**	

*Modified from the Statistical Review and Evaluation as of March 8, 2023[7]

Abbreviations: CI = confidence interval; LS = least squares; NOV03 = perfluorohexyloctane; SD = standard deviation; tCFS = total corneal fluorescein staining; VAS = visual analog scale

The clinical reviewer concluded that perfluorohexyloctane has provided clinically relevant and statistically significant evidence that perfluorohexyloctane can help patients achieve improvements in both signs and symptoms of their DED. [e] The clinical reviewer noted the efficacy data did not show a specific benefit to the MGD population over the broader population, therefore, the indication will be for a broader DED population, not limited to DED with MGD.[8,]

5. Risk Assessment & Safe-Use Conditions

The safety database includes 614 patients exposed to at least one dose of perfluorohexyloctane from two phase 3 studies, Study NVU-003 (n=303) and Study BL-904 (n=311). Blurred vision (3%) was the most commonly reported adverse event in ≥ 2% of participants receiving perfluorohexyloctane compared to saline (1.4%).[f] No deaths occurred in any of the clinical trials during the treatment period.

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition.*

[f] Section 505-1 (a) of the FD&C Act: *FDAAA factor (E): The seriousness of any known or potential adverse events that may be related to the drug and the background incidence of such events in the population likely to use the drug.*

None of the patients in the two phase 3 studies had an ocular serious adverse reaction[g] (SAR). Three (3) patients treated with perfluorohexyloctane had non-ocular SARs including diverticulum, endometrial adenocarcinoma, and spontaneous abortion. According to the Applicant, no SARs are related to the drug. Overall, the clinical reviewer agreed with the Applicant's conclusions including conveying the risk of blurred vision in Section 6, Adverse Events of the prescribing information.

6. Expected Postmarket Use

Perfluorohexyloctane is likely to be prescribed by primary care clinicians and eye care specialists and is expected to primarily be used by patients in the outpatient setting. If approved, perfluorohexyloctane will be the first semifluorinated alkane approved for the use of dry eye. Other approved ophthalmic products for the treatment of dry eye disease have a similar risk profile, therefore healthcare providers who are likely to prescribe perfluorohexyloctane should be familiar with the risks.

7. Risk Management Activities Proposed by the Applicant

The Applicant did not propose any risk management activities for perfluorohexyloctane beyond routine pharmacovigilance and labeling.

8. Discussion of Need for a REMS

The clinical reviewer recommends approval of perfluorohexyloctane on the basis of the efficacy and safety information currently available.[8]

Perfluorohexyloctane is a semifluorinated alkane proposed for treatment of DED associated with MGD. DED is a disorder characterized by reduced film production or tear film instability which results in symptoms of discomfort, visual disturbance, and inflammatory disease of the ocular surface. DED disease is associated with irritation, itching, soreness, ocular discomfort, burning, or intermittent blurred vision that may become constant as well as potentially disabling in severe disease.

As there are no approved treatments designed to cure the disease, there remains an unmet need for treatment options for DED. Perfluorohexyloctane offers an additional option for patients who are unable to receive, tolerate, or adequately benefit from currently available therapies. The use of perfluorohexyloctane resulted in statistically significant improvements in tCFS score and in the VAS dryness score. During the course of the review, it was determined that the efficacy data did not support limiting the approval of the indication to DED with MGD; therefore, the indication was revised to "perfluorohexyloctane is indicated for treatment of the signs and symptoms of dry eye disease."[1] The

[g] Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization, or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Division of Ophthalmology determined that there is substantial evidence of effectiveness that perfluorohexyloctane improves signs and symptoms of DED with an acceptable safety profile.

Perfluorohexyloctane is associated with a risk of blurred vision. This risk will be communicated through labeling. Based on the available safety information, this reviewer concluded that a REMS is not necessary to ensure the benefits outweigh the risks.

9. Conclusion & Recommendations

The clinical reviewer has determined that the benefit-risk assessment for perfluorohexyloctane supports approval.

Based on the available safety information, the benefit-risk profile is favorable, and a REMS is not necessary for perfluorohexyloctane to ensure the benefits outweigh the risks. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

Should the Division of Ophthalmology have any concerns or questions or if new safety information becomes available, please send a consult to DRM.

10. Appendices

10.1. References

1. Bausch & Lomb Inc. DRAFT Meibo (perfluorohexyloctane) Prescribing Informaton as edited by FDA. *NDA 216675*. Accessed March 9, 2023;
2. Bausch & Lomb Inc. Clinical Overview for perfluorohexyloctane. *NDA 216675*. June 28, 2022
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4. Sheppard J, Shen Lee B, Periman LM. Dry eye disease: identification and therapeutic strategies for primary care clinicians and clinical specialists. *Annals of medicine (Helsinki)*. 2023;55(1):241-252. doi:10.1080/07853890.2022.2157477
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7. Zhou Y. Division of Biometrics IV. Statistical Review and Evaluation for Clinical Studies for NDA 216675. *NDA 216675*. February 28, 2023
8. Rose S. Division of Ophthalmology. DRAFT Clinical Review of perfluorohexyloctane. *NDA 216675*. March 06, 2023

10.2. Table 1. Drugs Approved in the US for Dry Eye Disease

Name (generic); Approval Year	Indication	Formulation(s)	Safety and Tolerability Issues	Risk Management Approaches
Increase Tear Production				
Restasis (cyclosporine ophthalmic emulsion); 2002	A calcineurin inhibitor immunosuppressant indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca	Ophthalmic emulsion	• potential for eye injury and contamination from vial touching the eye or any surface • should not be administered while wearing contact lenses	Labeling – Warning and Precaution
Cequa (cyclosporine ophthalmic solution); 2018	A calcineurin inhibitor immunosuppressant indicated to increase tear production in patients with keratoconjunctivitis sicca (dry eye)	Ophthalmic solution	• potential for eye injury and contamination from vial touching the eye or any surface • should not be administered while wearing contact lenses	Labeling – Warning and Precaution
Treat Signs and Symptoms				
Xiidra (lifitegrast); 2016	A lymphocyte function associated antigen-1 (LFA-1) antagonist indicated for the treatment of the signs and symptoms of dry eye disease (DED)	Ophthalmic solution	• Instillation-site irritation, dysgeusia, and reduced visual acuity	Labeling – Adverse Reactions
Eysuvis (loteprednol etabonate); 2020	A corticosteroid indicated for the short-term (up to two weeks) treatment of the signs and symptoms of dry eye disease	Ophthalmic suspension	• delayed healing and corneal perforation • intraocular pressure increase • cataracts • bacterial infections • viral infections • fungal infections • risk of contamination • contact lenses should be removed prior to instillation of Eysuvis and may	Labeling – Warning and Precaution

			be reinserted 15 minutes following administration	
Tyrvaya (varenicline); 2021	A nasal spray is indicated for the treatment of the signs and symptoms of dry eye disease	Nasal spray	Sneezing, cough, throat irritation, and instillation-site irritation	Labeling – Adverse Reactions

Source: Information obtained from labeling from Drugs@FDA

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/s/

CARLA C DARLING
05/18/2023 03:32:22 PM

JACQUELINE E SHEPPARD
05/18/2023 03:43:38 PM

LAURA A ZENDEL
05/18/2023 04:03:58 PM