

Differentiated Treatments for Dry Eye Disease (DED)

Whether DED presents as evaporative, inflammatory, or both, physicians have a variety of tools in their treatment armamentarium.



**BRANDON D.
AYRES, MD**



**DAMON DIERKER,
OD, FAAO**



**PREEVA K.
GUPTA, MD**



**JESSICA STEEN,
OD, FAAO**

Differentiated Treatments for Dry Eye Disease (DED)

Whether DED presents as evaporative, inflammatory, or both, physicians have a variety of tools in their treatment armamentarium.

PARTICIPANTS

BRANDON D. AYRES, MD

- Co-Director, Cornea Fellowship Program at Wills Eye Hospital, Philadelphia, PA
- Private practice, Ophthalmic Partners, Philadelphia, PA
- Member, CRST Editorial Advisory Board
- bayres@willseye.org
- Financial disclosure: Speaker (Bausch + Lomb); Consultant (Alcon, Bausch + Lomb, Carl Zeiss Meditec, W.L. Gore & Associates)

DAMON DIERKER, OD, FAAO

- Director of Optometric Services at Eye Surgeons of Indiana, Indianapolis, IN
- Member, Modern Optometry Editorial Advisory Board
- damon.dierker@esi-in.com
- Financial disclosure: Speaker (Bausch + Lomb); Consultant (AbbVie, Alcon, Bausch + Lomb, Bio-Tissue, Dompe, Nusight Medical, QuidelOrtho, etc.)

PREEYA K. GUPTA, MD

- Founder and Director of Triangle Eye Consultants, Raleigh, NC
- Member, CRST Editorial Advisory Board
- preeyagupta@gmail.com
- Financial disclosure: Speaker (Bausch + Lomb); Consultant (AbbVie/Allergan, Alcon, Bausch + Lomb, Johnson & Johnson Vision, Kala Pharmaceuticals, etc.)

JESSICA STEEN, OD, FAAO

- Associate Professor and Director of the Glaucoma Service at Nova Southeastern University College of Optometry, Fort Lauderdale, Florida
- jessica.steen@gmail.com
- Financial disclosure: Speaker (Carl Zeiss Meditec, Bausch + Lomb, Viatris, Thea Pharma, Alcon, AbbVie/Allergan, Astellas); Consultant (Bausch + Lomb, etc.)

THE MECHANISM AND PRESENTATION OF DED

Brandon D. Ayres, MD: We have gathered for a roundtable discussion about the etiology of dry eye disease (DED) and how new data may redefine our understanding of its process and our clinical treatment strategies. In 2023, the American Academy of Ophthalmology updated its DED preferred practice guidelines to highlight increased tear evaporation as a core mechanism of tear film instability.¹ We were taught that there are two primary forms of DED: evaporative dry eye and aqueous tear deficiency dry eye. We have since learned that evaporative DED is more prominent, with about 90% of our patients having either evaporative or mixed-mechanism disease.² I see this preponderance of evaporative DED in my practice. What do you all see in your practices?

Damon Dierker, OD, FAAO: I agree; I think DED presents on a spectrum,

and its diagnosis and treatment should be considered in this context. What I predominantly see in my practice might be called mixed-mechanism DED, but it's all tear film instability, and it doesn't exist in a silo.

Preeya K. Gupta, MD: Trying to tease out evaporative versus aqueous-deficient pathology can be complex, but we

have assessment tools to help us make treatment decisions. I think it's important to recognize evaporation and aqueous deficiency as important foundational categories of DED, but we need to address all signs and symptoms of the disease.

Jessica Steen, OD, FAAO: I find that most of my patients have predominantly evaporative DED. Treating these

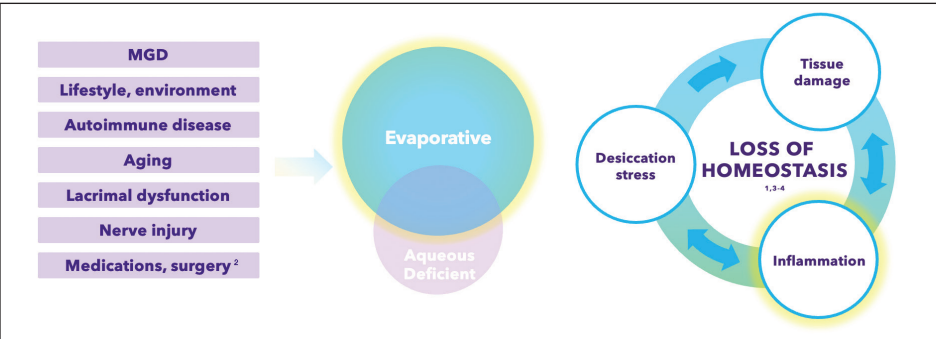


Figure 1. DED is a vicious cycle with many possible entry points. 1. Bron AJ, et al. *Ocul Surf*. 2017;15(3):438-510. 2. Galor A, et al. *Ocul Surf*. 2023;28:262-303. 3. Pflugfelder SC, et al. *Ophthalmology*. 2017;124(11S):S4-S13. 4. Zhang R, et al. *Ocul Surf*. 2021;21:145-159.

patients effectively begins with an accurate assessment and diagnosis, an understanding of the patient's past experiences—both their successes and challenges with treatment—and understanding of the underlying disease processes in order to determine the best treatment options in a truly individualized way.

"We need to educate our patients that they don't need to suffer with these symptoms—we have the tools to help them."

- Brandon D. Ayres, MD

Dr. Ayres: DED is unlike other diseases in eye care because there is no single source of its etiology. What we see on the ocular surface is the end expression of multiple factors (Figure 1). It can be subdivided into different mechanisms and etiologies—meibomian gland dysfunction (MGD), environmental influences, nutritional deficiencies, etc. Even when we confirm excessive tear evaporation, underneath it, there's still an inflammatory component (Figure 2). We must determine whether the inflammation is chronic or acute in order to prescribe the appropriate treatment.

The first ocular surface anti-inflammatory, cyclosporine, was approved in 2003.³ Since then, all anti-inflammatories (including XIIDRA® [lifitegrast ophthalmic solution 5.0%], the first pharmaceutical in the LFA-1 antagonist class, approved for the treatment of the signs and symptoms of DED in 2016), and immunomodulators have targeted inflammation, while tear stimulants have addressed aqueous deficiency.

Thus, until recently, evaporative dry eye has not been specifically addressed by a prescription medication. We now have MIEBO (perfluorohexyloctane ophthalmic solution; Bausch + Lomb). MIEBO is the first FDA-approved medication to treat the signs and symptoms of DED that uniquely targets tear evaporation.⁴ Every patient in the MIEBO FDA clinical trial was selected for clinical signs of MGD, which I believe was a first. Study subjects had to have a history of DED and clinical signs of MGD, a key consequence of which is tear evaporation.

EXPANDING DED TREATMENT AWARENESS AND ACCESS

Dr. Ayres: DED is a problem among the US population. There are estimates that 38 million patients have DED,^{5,6} but only 1.2 million have a prescription medication,⁷ which means we have millions of potential patients who are self-diagnosing and are visiting their local pharmacy to choose a topical drop from the sea of OTC dry eye

medications. Those who are not getting relief from ocular dryness with OTC drops should see an eye care professional. This is a huge opportunity for us to get patients into our offices for real, lasting treatment. Left untreated, DED can progress, with symptoms worsening over time. We need to educate our patients that they don't need to suffer with these symptoms—we have the tools to help them.

Dr. Dierker: We must screen for DED in all patients, referred and routine, and we need to agree on a protocol for diagnosing and treating DED based on signs and symptoms. How can I counsel my cataract surgery team if I don't know what a patient's ocular surface looks like? Likewise for glaucoma, the decision to choose an eye drop, or a laser, or a MIGS procedure will be partially based on the health of their ocular surface. In my population in Indiana, DED is more common than not. I think there is a huge opportunity to educate the public about DED and offer effective treatment options. The patients who I put on topical prescription DED drops are so thankful to get relief. It feels great whenever I can help a patient who's tried and failed other approaches.

Dr. Gupta: I frequently encounter patients who are frustrated by their chronic symptoms, and they tell me they've seen three doctors or that they've tried every eye drop available at their local pharmacy. So, there's a little bit of a disconnect as to why these therapies we now have are not reaching those patients. I think we should start patients on a prescription topical therapy for DED more regularly. MIEBO and XIIDRA each have a

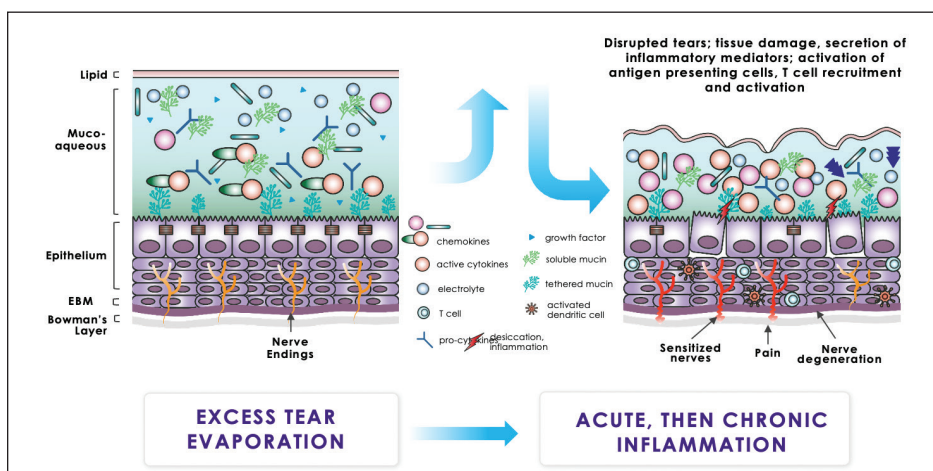


Figure 2. Regardless of etiology, excess evaporation leads to desiccation stress and damage.

Adapted from Perez VL, et al. *Exp Eye Res.* 2020;201:108294 and from Pflugfelder SC, de Paiva S. *Ophthalmology.* 2017;124(1S):S4-S13.

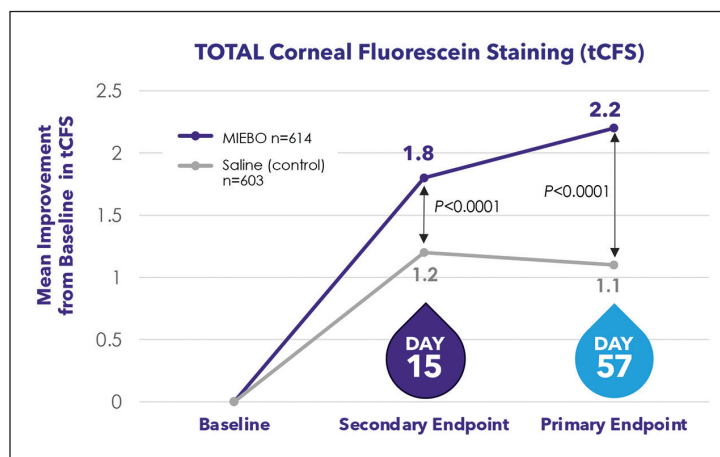


Figure 3. In its phase 3 clinical trials (GOBI¹ and MOJAVE²), MIEBO demonstrated improvement in total corneal fluorescein staining (tCFS) as early as day 15 and sustained through day 57. In the pooled dataset, the mean baseline tCFS for both MIEBO (n=614) and the control (saline; n=603) was 6.9. MIEBO recipients gained twice the improvement in corneal staining as the control by day 57 (the primary endpoint). (1. Tauber J, et al. *Ophthalmology*. 2023;130(5):516-524. 2. Sheppard JD, et al. *Am J Ophthalmol*. 2023;252:265-274.)

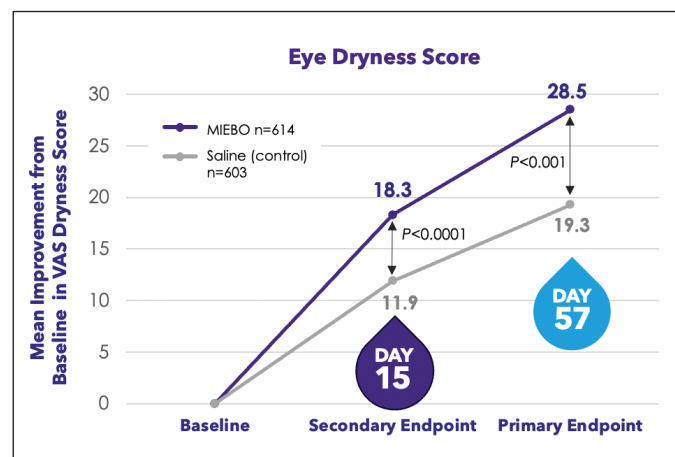


Figure 4. In its phase 3 clinical trials (GOBI¹ and MOJAVE²), MIEBO demonstrated relief from ocular dryness as early as day 15 and sustained through day 57. In the pooled dataset, the mean baseline eye dryness score on the Visual Analog Scale (VAS) was 65.6 for MIEBO (n=614) and 65.5 for saline (n=603). By day 57 (the primary endpoint), MIEBO recipients showed an improvement in ocular dryness that was 1.5 times greater than the saline control. (1. Tauber J, et al. *Ophthalmology*. 2023;130(5):516-524. 2. Sheppard JD, et al. *Am J Ophthalmol*. 2023;252:265-274.)

favorable safety profile, and I trust in the FDA's evaluation and approval process.

Dr. Steen: In my practice where most patients are using chronic topical ocular therapeutics related to the management of glaucoma, I find that addressing the ocular surface and the resulting improvement in the signs and symptoms of DED are key drivers to improve adherence in patients with both DED and glaucoma.

MIEBO EFFICACY AND PRACTICE PATTERNS

Dr. Ayres: MIEBO® (perfluorohexyloctane ophthalmic solution) has changed my practice pattern. I used to automatically prescribe an anti-inflammatory medication for any signs of DED. Now, if I see any signs of excessive tear evaporation, I prescribe MIEBO. It is the only FDA-approved DED medication that directly targets ocular surface evaporation. How do you each approach DED patients, and how might using MIEBO change your practice patterns?

Dr. Steen: Having the first and only approved medication to directly target tear evaporation has been a real call to action for eye care practitioners.

Dr. Dierker: There's no doubt that anti-inflammatory therapies will

continue to be a mainstay in DED management. Yet, having a topical drop that can reduce the rate of evaporation from the ocular surface could potentially qualify a greater number of candidates for treatment. With MIEBO now available, I would advise colleagues to avoid waiting until a patient's DED worsens to the point of corneal staining before prescribing a medication. For me, visually significant corneal staining is a low bar; often, the frequent use of artificial tears is enough for me to suggest a prescription medication.

Dr. Gupta: Having a pharmacological therapy that targets evaporation is a game-changer for how I approach patients. A treatment that can restrict tear evaporation is, to me, an important component in the DED treatment paradigm.

Dr. Dierker: The patient population recruited in the clinical trials for MIEBO is generally representative of what we see in our practices. Clinically, I see symptomatic patients who have MGD, obstruction in the meibomian glands, reduced tear break-up time (TBUT), and a compromised tear volume. Having a therapeutic that can address the signs I find is very helpful.

Dr. Gupta: Because no two dry eye patients come in with the same disease process, having treatments that target different pathways is so helpful to us as clinicians. Additionally, our treatments need to be effective and tolerable for patients. In its clinical trials, MIEBO demonstrated a clinically significant improvement in both the signs and symptoms of DED in as little as 2 weeks and through day 57.

In two phase 3 clinical studies, researchers evaluated the safety and efficacy of MIEBO for the treatment of DED. The GOBI⁸ and MOJAVE⁹ studies demonstrated that MIEBO works within 2 weeks, as noted above: there was a change in total corneal fluorescein staining from baseline at days 15 (secondary endpoint) and 57 (primary endpoint) (Figure 3). Similarly, MIEBO demonstrated a change from baseline in visual analog scale (VAS) dryness score at Days 15 (secondary endpoint) and 57 (primary endpoint) (Figure 4).

Furthermore, MIEBO proved to be user-friendly: patients in the studies reported that it was comfortable to use, and the most common adverse events were blurred vision upon instillation, which was mild and transient, and conjunctival redness which occurred at an incidence of 1-3%.⁴

Dr. Ayres: It's also important to remember that inflammation underlies DED. Fortunately, we now have two topical treatments: MIEBO® (perfluorohexyloctane ophthalmic solution) to address tear evaporation, and XIIDRA® (lifitegrast ophthalmic solution) 5.0% to address chronic inflammation. These therapies allow us to treat our DED patients in a more targeted fashion.

THE INFLAMMATORY COMPONENT OF DED

Dr. Ayres: Inflammation of the ocular surface has been the topic of DED for years. Early-generation anti-inflammatories were approved only to improve tear production, not necessarily to address the signs and symptoms of DED. Since 2016, we have had XIIDRA, which was uniquely designed as a topical anti-inflammatory to treat signs and symptoms of DED. While the exact mechanism of action is unknown, it is the only prescription therapy for signs and symptoms of DED that addresses active and inactive T-cells.^{10,11} Why is this impactful for treating DED?

Dr. Dierker: Our patients want symptomatic relief quickly. Thus, XIIDRA was game-changing—suddenly, I could say to my patients, “This drug designed specifically to treat dry eye disease has been approved for symptoms.” XIIDRA changed the conversation for me.

Unchecked tear film instability will eventually lead to inflammatory DED. When I identify patients who have inflammation, they often have conjunctival hyperemia and elevated levels of the inflammatory marker MMP-9. When I examine these patients’

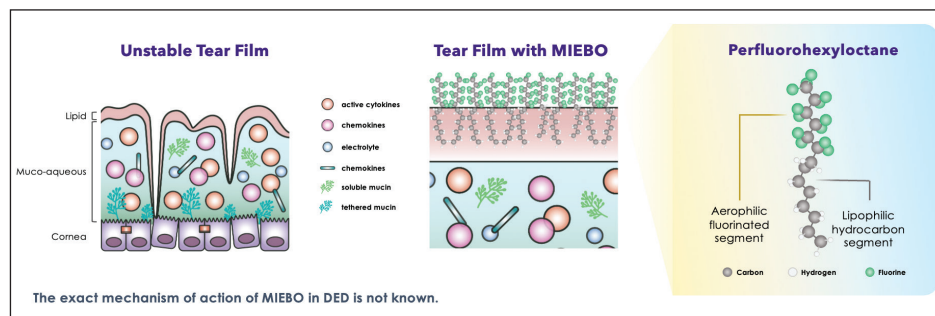


Figure 5. MIEBO forms a monolayer where the ocular tears meet the air to prevent surface evaporation.

lid margins, the need to address the inflammatory component is clear. XIIDRA remains the only topical nonsteroidal anti-inflammatory that can improve symptoms in as little as 2 weeks, as seen in 2 out of 4 clinical studies.¹⁰

Dr. Steen: The mechanism of action of XIIDRA is unique. It is able to disrupt the pathophysiology of the disease process on the immunomodulation level, and at a specific location, to impact not just the inactive T-cells but also the previously activated T-cells. I know XIIDRA is the only non-steroid prescription that can do that.

Dr. Gupta: I think the mechanism of action of XIIDRA enables it to work fast—in 2 out of 4 clinical trials, it was shown to be effective in as early as 2 weeks.¹⁰ Also, XIIDRA can inhibit migration of T-cells back to the ocular surface, thereby suppressing the inflammatory reaction early, and I think that's what really makes XIIDRA unique.

Dr. Ayres: I, too, like how fast XIIDRA can work. It is the only non steroid anti-inflammatory that has shown the abil-

ity to provide symptom relief in as little as 2 weeks in pivotal trials.¹⁰ And, while the exact mechanism of action is not known, it works on both active and inactive T-cells to decrease inflammation: its ability to block the interaction of lymphocyte function-associated antigen 1 (LFA-1) and intercellular adhesion molecule 1 (ICAM-1) not only suppresses the immune system from activating T-cells that are already circulating, it also suppresses already active T-cells from being drawn into the inflammatory site.¹⁰

THE MECHANISM OF ACTION OF MIEBO AND XIIDRA

Dr. Gupta: Here, we are going to talk about the mechanism of action of both MIEBO and XIIDRA. Dr. Ayres, how does MIEBO work?

Dr. Ayres: I am impressed by MIEBO. MIEBO is a single-ingredient medication, perfluorohexyloctane ophthalmic solution, that protects the tear film from evaporation. With this treatment, within 2 weeks we see improvement in the signs and symptoms of DED.

Dr. Steen: What makes MIEBO so unique is the molecule itself. It has two different components that make the molecule align in a specific way. The fluorinated component orients itself out into the environment, and the other component of the molecule inserts itself into the lipid layer. This creates a monolayer on the ocular surface that helps reduce evaporation, and so can help to improve tear film homeostasis and thus protect the ocular surface (Figure 5).

“What makes MIEBO so unique is the molecule itself. [It] creates a monolayer on the ocular surface that helps reduce evaporation.”

- Jessica Steen, OD, FAAO

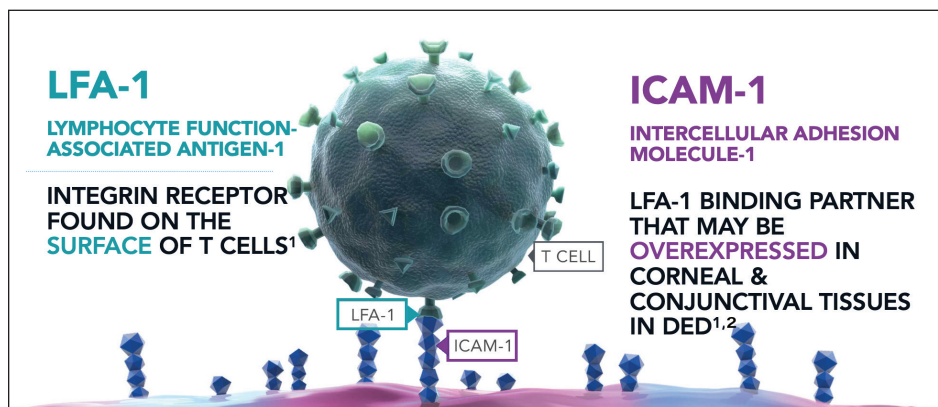


Figure 6. How XIIDRA blocks the cytokine storm caused by the interaction of ICAM-1 and LFA-1 in DED. The exact MOA is unknown.

1. XIIDRA prescribing information 2. Gao et al. *Exp Eye Res.* 2004;78(4):823-835, 510.

Dr. Dierker: MIEBO® (perfluorohexyloctane ophthalmic solution) created a new category of medication for signs and symptoms of DED. We know that excessive evaporation is almost universal in such patients, and now we have this single-ingredient, nonsteroidal, unpreserved, comfortable drop that targets evaporation.

Dr. Gupta: When we think about evaporation, we should consider the function of the meibum, which is to protect the ocular surface from tear evaporation. Something Dr. Steen said is very important to understand: perfluorohexyloctane, or PFHO, is a very different molecule than we're used to. It spreads across the ocular surface and helps to limit evaporation by forming a long-lasting monolayer. As I learned about the mechanism of MIEBO, it challenged me to think of other things we can do that help to limit tear evaporation. Has anyone else experienced an "aha" moment of understanding the tear film or how we approach it?

Dr. Dierker: MIEBO works differently than any other topical medication we've had. Other topical molecules must penetrate the tear film to reach the cornea and conjunctiva to work effectively. MIEBO inserts in the tear film, into the lipid layer, to provide that evaporative barrier and help prevent

moisture from getting out. It's a different way to look at its mechanism of action.

Dr. Steen: From a mechanistic standpoint, we usually take one of two approaches to the management of any disease process: we find the area of pathology and disrupt or alter that pathway in some way; or, as with MIEBO, we mimic the anti-evaporative function of natural meibum.

Dr. Gupta: The durability of MIEBO is really meaningful to me as a clinician, and I think it resonates with patients. MIEBO remains present on the ocular surface for at least 6 hours in PK rabbit studies, whereas artificial tears typically dissipate within a few minutes. The clinical significance of this is unknown.

Dr. Dierker: I use that same talking point with my patients, and it usually gets them on board with MIEBO. I explain that OTC lubricant eyedrops tend to only provide temporary relief.

Dr. Steen: Once the patient has started MIEBO therapy and then returns for that first follow-up visit, I always ask how their use of artificial tears has changed (I use the SPEED questionnaire to capture this subjective information). To me, a reduction in use of artificial tears is one indicator of the success of the treatment. For those who continue to use artificial tears, I counsel them not to instill

artificial tears immediately after MIEBO, because they could potentially impact the effectiveness of MIEBO. It's also important to note that MIEBO should not be administered while wearing contact lenses. Contact lenses should be removed before use and for at least 30 minutes after administration of MIEBO.

XIIDRA

Dr. Gupta: Let's now talk about XIIDRA® (lifitegrast ophthalmic solution) 5.0%, an LFA-1 antagonist. Dr. Dierker, please tell us how XIIDRA works.

Dr. Dierker: XIIDRA is an anti-inflammatory immunomodulator that targets a very specific interaction in patients with DED. In the presence of T-cell-mediated inflammation, intercellular adhesion molecule-1 (ICAM-1) is overexpressed on the ocular surface. On these T-cells, the lymphocyte function-associated antigen-1 (LFA-1) binds with ICAM-1, causing a cytokine storm. The molecule in XIIDRA is an antagonist to LFA-1 that blocks that interaction (Figure 6). Also, it impacts both active and inactive T-cells. XIIDRA is FDA-approved to treat the signs and symptoms of DED, and importantly, it gave some patients symptom relief within 2 weeks as seen in 2 out of 4 studies. It is the first immunomodulator to target a very specific part of the inflammatory pathway, as well as T-cells that are both active and inactive.

Dr. Gupta: There are many immunomodulators for us clinicians to choose from to treat DED. How do you know what to choose for your patient?

Dr. Steen: For me, it comes back to the clinical data to support each therapeutic option. In patients with clear signs of inflammation, the clinical data to support the onset of symptom relief in as little as 2 weeks, combined with an appropriate tolerability profile (Figure 7), is something that sways patients toward XIIDRA especially for those who have tried multiple products and seen multiple doctors.

“I agree with Dr. Gupta that we all need an efficient, reproducible protocol to screen for DED in each patient we see.”

- Damon Dierker, OD, FAAO

Dr. Ayres: Because there are multiple mechanisms of action contributing to DED, I like to conduct thorough preoperative testing—including tear film osmolarity, MMP-9, evaluating the meibomian glands and TBUT—to see if I can pinpoint where the dysregulation is. These data help me discern whether the patient needs help with the evaporative component or the inflammatory side of DED, or both. I find that exploring the ocular surface for this information is an exciting new frontier in the ocular surface world.

Dr. Dierker: I agree with Dr. Ayres about our approach to DED management, and I don't think we have to overthink it. MIEBO® (perfluorohexyloctane ophthalmic solution) and XIIDRA® (lifitegrast ophthalmic solution) 5.0%, work differently; their mechanisms of action are targeting ocular surface evaporation and inflammation, respectively. Yet,

they're both labeled to treat the signs and symptoms of DED, and either one is an appropriate therapy for many of our patients.

I think we can simply ask ourselves: are this patient's eyes clearly inflamed, or does the patient have a pro-inflammatory systemic disease that would indicate XIIDRA as the first-line therapy? Or, is this a patient who is in front of a computer all day, or who wears contact lenses, or experiences some other circumstance that will trigger evaporative stress in the ocular surface? They may not have a lot of systemic inflammation contributing to their ocular surface disease. We can treat them now with MIEBO. I think there's clearly room for both products, thanks to their labeling.

Dr. Gupta: Absolutely, there's room for both medications. When it comes to selecting which immunomodulator I like to use, I am compelled by the symptom

data. The reason I reach for lifitegrast often in my practice is because it works on both active and inactive T-cells. T-cells that are circulating in the blood have a 90-day life cycle. Traditional molecules like cyclosporine only work on the production of new T-cells, which is why patients often take a long time to respond to these older medications, because they still have circulating T-cells. XIIDRA works on T-cells that are in circulation, and it also slows down the activation of new T-cells. I think that is why we see symptom improvement as early as 2 weeks in some patients with XIIDRA.

CLINICAL CONSIDERATIONS FOR MANAGING DED PATIENTS

Dr. Dierker: Let's discuss the nuts and bolts of addressing DED in the clinic. How do we approach the dry eye patient? What does that workup look like? How do we choose between or combine our topical therapeutics?

Dr. Ayres, we'll start with you. Our practice settings may differ, but we're seeing patients with DED all day, every day. How are you screening for signs and symptoms of DED in your patient population?

Dr. Ayres: When a patient presents to our office, we begin by giving them a questionnaire (modified from validated studies) that asks them about fluctuations in their vision and other such symptoms. When it comes time for the physical examination, our technicians are trained to look for certain key signs, such as irregularity on a patient's topographic maps, that require my assessment.

The patients who have not received a previous diagnosis of DED are usually surprised when we tell them we will prioritize improving those symptoms before we address the issue they originally came in for.

Dr. Dierker: Dr. Steen, with your glaucoma-based population, how are you assessing signs and symptoms and making the differential diagnosis of DED? What does your screening process look like?

XIIDRA demonstrated tolerability

Across 5 clinical studies, most common adverse reactions (reported in 5% to 25% of patients)¹

- instillation site irritation
- dysgeusia
- reduced visual acuity

• TEAEs that led to discontinuation²

- 7.0% (90/1287) of participants on lifitegrast
- 2.6% (31/1177) of those receiving vehicle
- There were no serious ocular TEAEs and no serious nonocular TEAEs considered related to treatment²

Among lifitegrast-treated participants in a 1-year safety study & a pooled analysis of four 12-week studies²

<2% discontinued due to dysgeusia

≤1% discontinued due to instillation site irritation or pain

<2% discontinued due to instillation site reaction

Figure 7. XIIDRA was well-tolerated across five clinical studies.

1. XIIDRA prescribing information. 2. Nichols KK, et al. *Eur J Ophthalmol*. 2019;29(4):394-401.

Courtesy of Preeya Gupta, MD

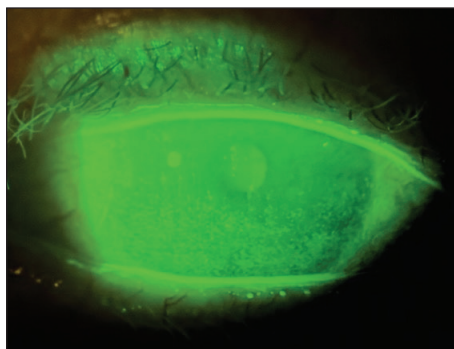


Figure 8. Dr. Gupta uses fluorescein staining to assess the health of the ocular surface.

Dr. Steen: Most of my patients present for ongoing care related to a glaucoma diagnosis, or are referred for assessment for suspicion of glaucoma, or are seeking a second opinion related to treatment or management of glaucoma. However, whether the patient is already on topical glaucoma therapy or needs to begin it, my team and I ensure that their ocular surface is optimized to allow for healthy ongoing topical therapy with maximal adherence.

Similar to Dr. Ayres, I use a validated questionnaire, the SPEED questionnaire. I also include fluorescein corneal staining, lissamine green conjunctival staining, and a careful evaluation of the eyelids and tear meniscus height.

Dr. Gupta: My routine protocols are very similar. I think the key is being consistent in how we approach these patients. If I could only pick two things to screen for DED, I'd ask the patient if they were using an artificial tear, because a lot of patients don't consider this a form of treatment. In my opinion, if somebody is going out of their way to use drops, then they have real disease.

Secondly, using a 10-cent fluorescein strip gives me a wealth of information. I can assess the TBUT, look for corneal staining (Figure 8), examine the pattern of the dye across the surface, and check if there are any contributing lid abnormalities. I use the strip the same way every single time for all types of patients who come into my practice, and it has helped me to find the disease quite often.

Dr. Dierker: I agree with Dr. Gupta that we all need an efficient, reproducible protocol to screen for DED in each patient we see. It sounds like we all use targeted questions and look for symptoms, because DED is a symptomatic disease. We also look for loss of corneal homeostasis, whether that's increased tear osmolarity or putting fluorescein in the eye and looking at the TBUT or ocular surface staining.

Dr. Steen, you mentioned that DED often starts from abnormalities in the eyelid, whether it's inflammation, obstruction, or both. How do you assess eyelids in your clinic?

Dr. Steen: I have a methodical approach to assessing the meibomian glands, specifically. It starts with looking at the lid itself. Is the eyelid positioned where I expect it to be? Is there a significant entropion, ectropion, or eyelid laxity? Looking at the tear meniscus height is something I find truly valuable, as well. Then, I push on the lower lid, starting just nasal to the center of the eyelid with firm pressure on the tarsal plate to see if there is meibomian gland secretion and to assess the quality of the secretion. Does it look healthy, is it turbid, thickened, or absent?

Dr. Ayres: Expressing the meibomian glands gives us so much information about the patient's ocular surface health. At Will's Eye Hospital, we're all trained to use cotton tip applicators, even if someone doesn't have a single symptom of DED. For every single patient, I put a little pressure on the tarsal plate and note the meibomian gland secretions.

Dr. Gupta: Dr. Ayres and I were both on the Cornea Clinical Committee for the ASCRS, and we came up with a little mnemonic device—LLPP—to evaluate the ocular surface efficiently. LLPP stands for: look at the lids; lift the lids to look for any corneal pathology or superior conjunctival pathology; and then pull and push. (*Pull* the upper lid looking for laxity. *Push* refers to pushing the meibomian glands to look at their secretion). The mnemonic device helps us remember to include it in each examination.

Dr. Dierker: I like that: look down, look up, press—those steps may only take 5 or 10 seconds. To ignore the eyelids as part of a comprehensive examination is to ignore one of the most common reasons patients schedule time to see us: because they have sequela related to an eyelid problem.

Dr. Ayres: As I alluded to previously, I often diagnose DED in a patient while I'm evaluating them for another reason. Now the patient has two diagnoses, and my priority is to rapidly rehabilitate the ocular surface. If their DED is primarily inflammatory, I will reach for XIIDRA® (lifitegrast ophthalmic solution) 5.0%. If I think it's primarily evaporative, I will reach for MIEBO® (perfluorohexyloctane ophthalmic solution). That patient will begin these treatments and then transition back to their primary eye care team for follow-up until their ocular surface is healthy enough for surgery. If they don't continue that therapy, we won't see improvement. How do each of you communicate the need for ongoing DED management to your referring physicians?

"My team and I don't accept corneal staining in our perioperative patients, and we shouldn't accept corneal staining in our routine care, either, because we know it's going to compromise patients' vision."

- Preeya K. Gupta, MD

CASE STUDY

Dr. Steen: We've had an opportunity to talk about DED, how each of us diagnoses the disease process, and our approaches to treatment strategies. Now, we get to bring it home and talk about specific patient cases. **Dr. Ayres,** tell us about a particular case that you treated recently.

SEVERE OSD BEFORE CATARACT SURGERY

Dr. Ayres: This is a patient whom my team and I have been treating for a long time, and her presentation will sound familiar to many of you. She was interested in gaining better vision through cataract surgery, but she presented with myriad ocular surface problems, starting with severe anterior basement membrane corneal dystrophy (Figure 1).

This patient's medical history included previous keratectomies to remove the surface irregularities, which uncovered significant OSD, primarily evaporative (Figure 2). We told this individual that

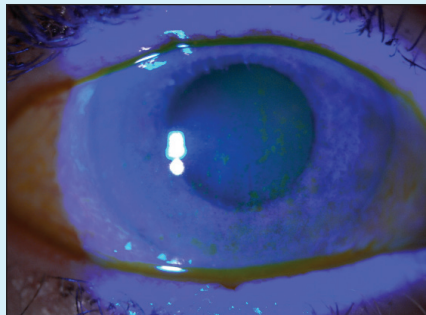


Figure 1. The preoperative clinical examination revealed a high degree of corneal staining.

we'd have to delay her cataract surgery until her ocular surface was healthy enough.

She exhibited true DED—not just punctate epithelial erosions along the inferior cornea, but irregular corneal topographies right up into the visual axis. When this patient began her journey, we didn't have MIEBO® (perfluorohexyloctane ophthalmic solution), so I originally prescribed a typical course of anti-inflammatory medication, but her TBUT remained at approximately 5 seconds with corneal staining. I switched her to MIEBO once it became available, and I saw a significant improvement within just a few weeks, not only in her symptoms, but importantly, in her clinical signs. I was finally able to say that this patient was a candidate for cataract surgery. In cases of evaporative DED like this, I am now using MIEBO as an early intervention. It really helps improve the ocular surface so that patients like this one can move toward their ultimate goal.

Dr. Dierker: Clearly, you had identified this patient as having visually significant OSD, which is an important distinction. Topographic changes due to DED may impact surgical planning. Could

this patient have been a candidate for XIIDRA® (lifitegrast ophthalmic solution) 5.0%, as well? XIIDRA has been shown to improve biometric and keratometric measurements in as little as 4 weeks. I'm interested why you chose MIEBO in this case, because I think you could make the argument for either medication.

Dr. Ayres: This patient had already been on immunomodulators in the past, and she had not experienced enough of an improvement. I think that using an anti-inflammatory in this patient was a necessary step, but it wasn't sufficient to get her across the finish line. Thus, I switched to MIEBO to reach that goal.

Dr. Steen: How is this patient going to be managed postoperatively, long-term?

Dr. Ayres: This patient did well after her surgery (Figure 3). She gained a significant improvement in her vision, but we cannot back off on the surface treatment, or else her corneas may regress. She already knows she has DED that requires ongoing management, but we try to mitigate symptoms as much as possible.

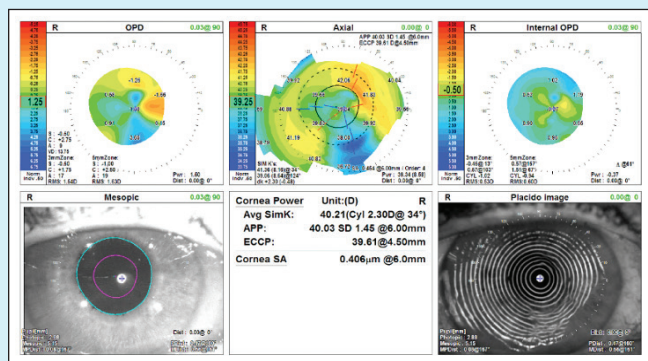


Figure 2. The patient's preoperative topography showed high levels of irregular astigmatism due to OSD.

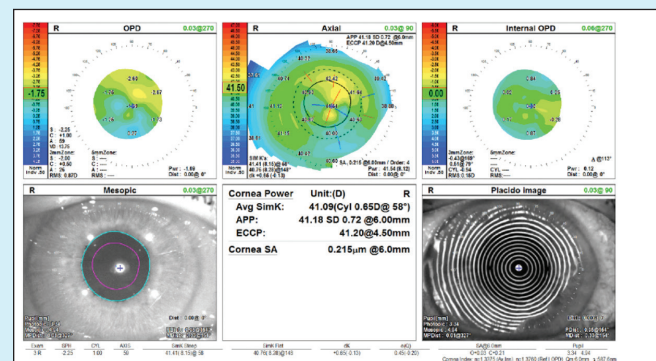


Figure 3. One month after the patient initiated MIEBO drops, her corneal topography was much improved.

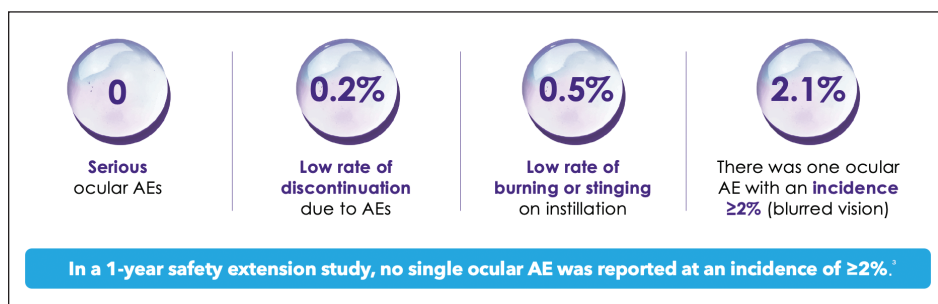


Figure 9. In two pivotal clinical trials (phase 3 GOBI¹ and phase 3 MOJAVE²), a total of 1217 patients were randomized 1:1 to receive either MIEBO (n=614) or hypotonic (0.6%) saline (n=603) QID for 8 weeks. Most ocular AEs were considered mild (most common was blurred vision), and discontinuation rates due to AEs for MIEBO were comparable to the control (pooled: 0.2% vs 0.5%, respectively). In total, one patient in the MIEBO arm (out of 614) discontinued due to eye irritation. (1. Tauber J, et al. *Ophthalmology*. 2023;130(5):516-524. 2. Sheppard JD, et al. *Am J Ophthalmol*. 2023;252:265-274. 3. Protzko EE, et al. *Cornea*. 2024;43(9):1100-1107.).

Dr. Gupta: I think it starts with the patient. I always try to impress on the patient all the things that are causing their blurred vision and the need for ongoing treatment. The patient's buy-in is primary.

With referring physicians, I believe in maintaining open lines of communication. All of my referring doctors have my cell phone number and our office number if there's a question or problem. Yet, I still see patients who have discontinued their therapy.

Dr. Dierker: I think you've hit on it: it's consistency. We have to make patients' ocular health a priority. I think there's an opportunity for both optometrists and ophthalmologists to do a better job with that.

TREATMENT STRATEGIES

Dr. Dierker: Let's say we have a patient who has signs and symptoms of DED in the presence of MGD. How do you determine your treatment strategy between evaporative therapy and inflammatory therapy?

Dr. Gupta: First, we must determine whether the patient is currently using any treatments or not. Then, corneal staining is key, to me—it means that they have moderate-level disease or worse. My team and I don't accept corneal staining in our perioperative patients, and we shouldn't accept corneal staining in our routine care, either, because we know it's going to compromise patients' vision.

When I see corneal staining, I anticipate an excessive amount of inflammation on the ocular surface. If this patient is not currently using any therapeutic, I'll tell them that we'll start with one topical medication and keep adding drops until the corneal staining resolves. But then, there's also the symptomatic component.

If there are a significant number of inflammatory signs—redness, breakdown of the corneal epithelium, staining of the conjunctiva—these are among the early findings of inflammatory DED. For those patients, I tend to lean toward the immunomodulator pathway as my initial therapy. Yet, many patients need more than one therapy, and you can't ignore the

evaporative component, as that may be an equal contributor to their disease process.

Dr. Dierker: Dr. Steen, what are the things in the patient's history, treatment goals, or clinical presentation that would make you choose MIEBO® (perfluorohexyloctane ophthalmic solution) as their first treatment?

Dr. Steen: As Dr. Gupta mentioned, the patient's history is important, and I also think about it from a systemic perspective. What systemic medications are they taking? What systemic conditions do they have that may have an impact on the immune system and may exacerbate signs and symptoms of dry eye disease? For example, diabetes mellitus is important to recognize, because of its potential impact on the ocular surface.

I ask about fluctuation in vision, especially toward the end of the day, to indicate too much evaporation. I also clinically assess for meibomian gland dysfunction, reduced TBUT, and I pay attention to the pattern of the tear break-up.

One of the highlights of the clinical trials assessing the safety and efficacy of MIEBO was its tolerability profile (Figure 9). For patients who may have stinging and burning upon instillation of other eye drops,¹² including artificial tears, I find that MIEBO is a medication that is comfortable.

Dr. Dierker: I agree that fluctuating vision has been a gap in our patients whose symptoms worsen later in the day. This symptom is common with evaporative dry eye. I also agree that MIEBO is very well tolerated, both in the clinical studies and in my patient population. It works quickly, too—within a couple of weeks.

Dr. Ayres, what does a candidate for XIIDRA® (lifitegrast ophthalmic solution) 5.0% look like for you and your practice?

Dr. Ayres: Inflammation is the core of DED. When we clinicians are trying to decide whether to treat the inflammation or the evaporation first, for me, it comes down to clinical testing and the physical examination. The inflamed eye may have superficial punctate keratitis. Remember,

"Until we had MIEBO, we had no prescription eye drop that addressed the excessive tear evaporation caused by MGD."

- Brandon Ayres, MD

a patient with an epitheliopathy anywhere on the cornea deserves an anti-inflammatory. That was the clinical rule I learned in training and still follow.

The question of what to start patients on is becoming a bigger issue. Very few patients these days are on a single medication, and polypharmacy in DED is very common. This may include a prescription anti-inflammatory and something like MIEBO® (perfluorohexyloctane ophthalmic solution), or maybe it's an autologous serum plus amniotic cytokine extract drops. I am very quick to prescribe an immunomodulator such as XIIDRA® (lifitegrast ophthalmic solution) 5.0%. XIIDRA works well, and it's been proven in multiple studies. If inflammation is the key part of a patient's DED, I'm going to start with XIIDRA.

Dr. Dierker: Dr. Gupta, how do XIIDRA and MIEBO mesh with other DED therapies patients may be using: nutritional supplements, in-office therapies with light or thermal applications, etc.?

Dr. Gupta: My staff and I do a lot of interventional procedures in the office for MGD, and I think they are complementary for the appropriate patients. I love doing those procedures to jumpstart the function of the glands and support the anti-evaporative effects of MIEBO. For patients who have mild disease, a topical therapy may be all they need. Some patients need the combination of a pharmaceutical and an adjunctive procedure, and some patients need all three categories of treatments you mentioned. Managing DED is a journey we take with the patient over time.

Dr. Ayres: Until we had MIEBO, we had no prescription eye drop that addressed the excessive tear evaporation caused by MGD. Interventional dry eye therapy is still a big part of my practice, as is using MIEBO. They are not mutually exclusive.

Dr. Dierker: It's the same for me. And, if I've started a patient on an in-office DED treatment and I still see inflammation or

poor-quality meibomian gland secretions on follow-up, it's very easy to add XIIDRA or MIEBO. Although there is no clinical study on the simultaneous use of MIEBO and XIIDRA, they are not contraindicated. ■

1. Amescua G, Ahmad S, Cheung AY, et al: American Academy of Ophthalmology Preferred Practice Pattern Cornea/External Disease Committee. Dry eye syndrome PPP 2023. Accessed July 30, 2024. <https://www.aao.org/education/preferred-practice-pattern/dry-eye-syndrome-ppp-2023>.
2. Lemp MA, Crews LA, Bron AJ, et al. *Cornea*. 2012;31:472-478.
3. Restasis approval package. Center for Drug Evaluation and Research. Accessed July 30, 2024. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-023_Restasis_Approv.PDF.
4. MIEBO. Prescribing Information. Bausch + Lomb, Inc.; 2023. Accessed August 27, 2024. <https://pi.bausch.com/globalassets/pdf/packageinserts/pharma/miebo-package-insert.pdf>.
5. Paulsen AJ, Cruickshanks KJ, Fischer ME, et al. Dry eye in the beaver dam offspring study: prevalence, risk factors, and health-related quality of life. *Am J Ophthalmol*. 2014;157(4):799-806.
6. Farrand KF, Fridman M, Stillman IO, Schaumberg DA. Prevalence of diagnosed dry eye disease in the United States among adults aged 18 years and older. *Am J Ophthalmol*. 2017;182:90-98.
7. Karpecki PM, Nichols KK. Addressing excessive evaporation: an unmet need in dry eye disease. Supplements and featured presentations. *Am J Manag Care*. 2023; 29:S239-S247. Accessed August 27, 2024. <https://doi.org/10.37765/ajmc.2023.89448>.
8. Tauber J, Berdy GJ, Wirta DL, et al. NOV03 for dry eye disease associated with meibomian gland dysfunction: Results of the randomized phase 3 GDBI study. *Ophthalmology*. 2023;130(5):516-524.
9. Sheppard J, 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 Ophthalmology*. 2023;252:265-274.
10. XIIDRA. Prescribing information. Bausch + Lomb, Inc.; 2020. Accessed August 27, 2024. https://www.novartis.com/us-en/sites/novartis_us/files/xiidra.pdf.
11. Perez VL, Pflugfelder SC, Zhang S, et al. Lifitegrast, a novel integrin antagonist for treatment of dry eye disease. *Ocul Surf*. 2016;14(2):207-215.
12. de Paiva CS, Pflugfelder SC, Ng SM, et al. Editor: Cochrane Eyes and Vision Group. Topical cyclosporine A therapy for dry eye syndrome. *Cochrane Database Syst Rev*. 2019(9):CD010051.

MBO.0597.USA.24

INDICATION

Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of signs and symptoms of dry eye disease (DED).

IMPORTANT SAFETY INFORMATION

- Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients.
- In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.
- To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.
- Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.
- Safety and efficacy in pediatric patients below the age of 17 years have not been established.

Please see accompanying full Prescribing Information for XIIDRA

INDICATION

MIEBO® (perfluorohexyloctane ophthalmic solution) is indicated for the treatment of the signs and symptoms of dry eye disease.

IMPORTANT SAFETY INFORMATION

- MIEBO should not be administered while wearing contact lenses. Contact lenses should be removed before use and for at least 30 minutes after administration of MIEBO
- Instruct patients to instill one drop of MIEBO into each eye four times daily
- The safety and efficacy in pediatric patients below the age of 18 have not been established
- The most common ocular adverse reaction was blurred vision (1% to 3% of patients reported blurred vision and conjunctival redness)

Please see accompanying full Prescribing Information for MIEBO

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use XIIDRA safely and effectively. See full prescribing information for XIIDRA.

XIIDRA® (lifitegrast ophthalmic solution), for topical ophthalmic use
Initial U.S. Approval: 2016

INDICATIONS AND USAGE

Xiidra (lifitegrast ophthalmic solution) 5% is a lymphocyte function-associated antigen-1 (LFA-1) antagonist indicated for the treatment of the signs and symptoms of dry eye disease (DED). (1)

DOSAGE AND ADMINISTRATION

One drop twice daily in each eye (approximately 12 hours apart). (2)

DOSAGE FORMS AND STRENGTHS

Ophthalmic solution containing lifitegrast 50 mg/mL (5%). (3)

CONTRAINDICATIONS

Hypersensitivity. (4)

ADVERSE REACTIONS

The most common adverse reactions (incidence 5%-25%) following the use of Xiidra were instillation-site irritation, dysgeusia, and decreased visual acuity. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bausch & Lomb Incorporated at 1-800-553-5340 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience
- 6.2 Postmarketing Experience

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.2 Lactation
- 8.4 Pediatric Use
- 8.5 Geriatric Use

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

2 DOSAGE AND ADMINISTRATION

Instill one drop of Xiidra twice daily (approximately 12 hours apart) into each eye using a single-use container. Discard the single-use container immediately after using in each eye.

Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

3 DOSAGE FORMS AND STRENGTHS

Ophthalmic solution containing lifitegrast 50 mg/mL (5%).

4 CONTRAINDICATIONS

Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation [see *Adverse Reactions* (6.2)].

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity [see *Contraindications* (4)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In five clinical trials of DED conducted with lifitegrast ophthalmic solution, 1401 patients received at least one dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had less than or equal to 3 months of treatment exposure. One hundred-seventy patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5%-25% of patients were instillation-site irritation, dysgeusia, and reduced visual acuity.

Other adverse reactions reported in 1%-5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus, and sinusitis.

6.2 Postmarketing Experience

The following adverse reactions have been identified during post-approval use of Xiidra. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Rare serious cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, urticaria, allergic conjunctivitis, dyspnea, angioedema, and allergic dermatitis have been reported. Eye swelling and rash have also been reported [see *Contraindications* (4)].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on Xiidra use in pregnant women to inform any drug-associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from premating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear [see *Clinical Pharmacology* (12.3)].

Data

Animal Data

Lifitegrast administered daily by IV injection to rats, from premating through gestation day 17, caused an increase in mean pre-implantation loss and an increased incidence of several minor skeletal anomalies at 30 mg/kg/day, representing 5,400-fold the human plasma exposure at the RHOD of Xiidra, based on AUC. No teratogenicity was observed in the rat at 10 mg/kg/day (460-fold the human plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the RHOD, based on AUC), when administered by IV injection daily from gestation days 7 through 19. A fetal no observed adverse effect level (NOAEL) was not identified in the rabbit.

8.2 Lactation

Risk Summary

There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low [see *Clinical Pharmacology* (12.3)]. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra.

8.4 Pediatric Use

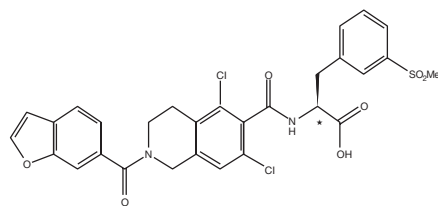
Safety and efficacy in pediatric patients below the age of 17 years have not been established.

8.5 Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and younger adult patients.

11 DESCRIPTION

The chemical name for lifitegrast is (S)-2-(2-(benzofuran-6-carbonyl)-5,7-dichloro-1,2,3,4-tetrahydroisoquinoline-6-carboxamido)-3-(3-(methylsulfonyl)phenyl)propanoic acid. The molecular formula of lifitegrast is $C_{28}H_{24}Cl_2N_2O_7S$ and its molecular weight is 615.5 g/mol. The structural formula of lifitegrast is:



*Chiral center

Lifitegrast is a white to off-white powder, which is soluble in water.

Xiidra (lifitegrast ophthalmic solution) 5% is a lymphocyte function-associated antigen-1 (LFA-1) antagonist supplied as a sterile, clear, colorless to slightly brownish-yellow colored, isotonic solution of lifitegrast with a pH of 7.0-8.0, and an osmolality range of 200-330 mOsmol/kg.

Xiidra contains Active: lifitegrast 50 mg/mL; Inactives: sodium chloride, sodium phosphate dibasic anhydrous, sodium thiosulfate pentahydrate, and water for injection. Sodium hydroxide and/or hydrochloric acid (to adjust pH).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lifitegrast binds to the integrin LFA-1, a cell surface protein found on leukocytes and blocks the interaction of LFA-1 with its cognate ligand intercellular adhesion molecule-1 (ICAM-1). ICAM-1 may be overexpressed in corneal and conjunctival tissues in DED. LFA-1/ICAM-1 interaction can contribute to the formation of an immunological synapse resulting in T-cell activation and migration to target tissues. *In vitro* studies demonstrated that lifitegrast may inhibit T-cell adhesion to ICAM-1 in a human T-cell line and may inhibit secretion of inflammatory cytokines in human peripheral blood mononuclear cells. The exact mechanism of action of lifitegrast in DED is not known.

12.3 Pharmacokinetics

In a subset of DED patients (n = 47) enrolled in a Phase 3 trial, the pre-dose (trough) plasma concentrations of lifitegrast were measured after 180 and 360 days of topical ocular dosing (one drop twice daily) with Xiidra (lifitegrast ophthalmic solution) 5%. A total of nine of the 47 patients (19%) had plasma lifitegrast trough concentrations above 0.5 ng/mL (the lower limit of assay quantitation). Trough plasma concentrations that could be quantitated ranged from 0.55 ng/mL to 3.74 ng/mL.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Animal studies have not been conducted to determine the carcinogenic potential of lifitegrast.

Mutagenesis

Lifitegrast was not mutagenic in the *in vitro* Ames assay. Lifitegrast was not clastogenic in the *in vivo* mouse micronucleus assay. In an *in vitro* chromosomal aberration assay using mammalian cells (Chinese hamster ovary cells), lifitegrast was positive at the highest concentration tested, without metabolic activation.

Impairment of Fertility

Lifitegrast administered at IV doses of up to 30 mg/kg/day (5400-fold the human plasma exposure at the RHOD of lifitegrast ophthalmic solution, 5%) had no effect on fertility and reproductive performance in male and female-treated rats.

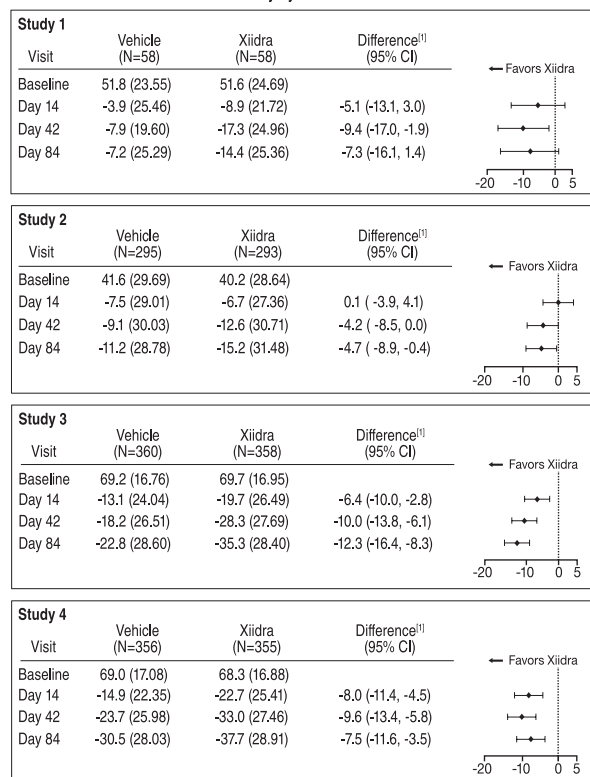
14 CLINICAL STUDIES

The safety and efficacy of lifitegrast for the treatment of DED were assessed in a total of 1181 patients (1067 of which received lifitegrast 5%) in four 12-week, randomized, multi-center, double-masked, vehicle-controlled studies. Patients were randomized to Xiidra or vehicle (placebo) in a 1:1 ratio and dosed twice a day. Use of artificial tears was not allowed during the studies. The mean age was 59 years (range, 19-97 years). The majority of patients were female (76%). Enrollment criteria included minimal signs (i.e., Corneal Fluorescein Staining and non-anesthetized Schirmer Tear Test) and symptoms (i.e., Eye Dryness Score (EDS) and Ocular Discomfort Score) severity scores at baseline.

Effects on Symptoms of Dry Eye Disease

Eye dryness score was rated by patients using a visual analogue scale (0 = no discomfort, 100 = maximal discomfort) at each study visit. The average baseline EDS was between 40 and 70. A larger reduction in EDS favoring Xiidra was observed in all studies at Day 42 and Day 84 (see Figure 1).

Figure 1: Mean Change (SD) From Baseline and Treatment Difference (Xiidra – Vehicle) in Eye Dryness Score in 12-Week Studies in Patients With Dry Eye Disease

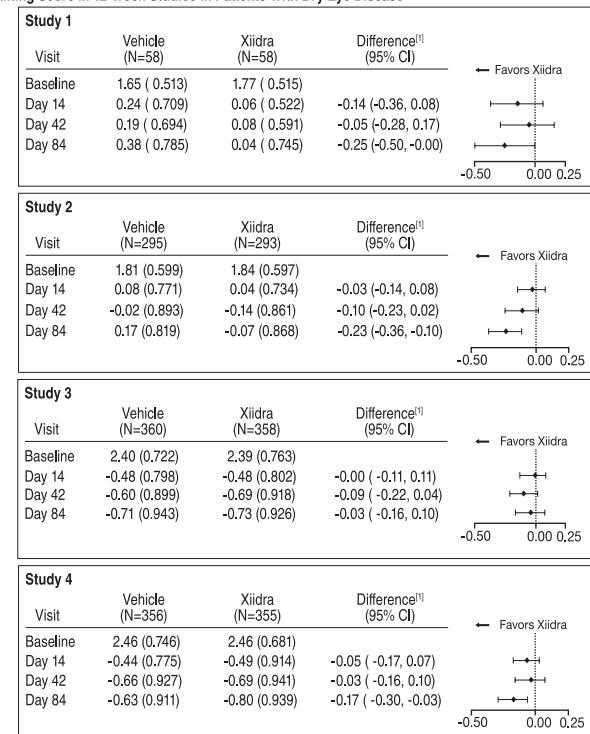


^[1] Based on analysis of covariance (ANCOVA) model adjusted for baseline value in Study 1, and ANCOVA model adjusted for baseline value and randomization stratification factors in Studies 2-4. All randomized and treated patients were included in the analysis and missing data were imputed using last-available data. In Study 1, one Xiidra-treated subject who did not have a baseline value was excluded from analysis.

Effects on Signs of Dry Eye Disease

Inferior fluorescein corneal staining score (ICSS) (0 = no staining, 1 = few/rare punctate lesions, 2 = discrete and countable lesions, 3 = lesions too numerous to count but not coalescent, 4 = coalescent) was recorded at each study visit. The average baseline ICSS was approximately 1.8 in Studies 1 and 2, and 2.4 in Studies 3 and 4. At Day 84, a larger reduction in ICSS favoring Xiidra was observed in three of the four studies (see Figure 2).

Figure 2: Mean Change (SD) From Baseline and Treatment Difference (Xiidra – Vehicle) in Inferior Corneal Staining Score in 12-Week Studies in Patients With Dry Eye Disease



^[1] Based on ANCOVA model adjusted for baseline value in Study 1, and ANCOVA model adjusted for baseline value and randomization stratification factors in Studies 2-4. All randomized and treated patients were included in the analysis and missing data were imputed using last-available data. In Study 2, one vehicle-treated subject who did not have a study eye designated was excluded from analysis.

16 HOW SUPPLIED/STORAGE AND HANDLING

Xiidra (lifitegrast ophthalmic solution) 5% (50 mg/mL) is supplied in a foil pouch containing 5 low-density polyethylene 0.2 mL single-use containers.

Carton of 60 single-use containers NDC 24208-911-12

Storage:

Store at 20°C to 25°C (68°F to 77°F). Store single-use containers in the original foil pouch.

17 PATIENT COUNSELING INFORMATION

Advise patients to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Handling the Single-use Container

Advise patients not to touch the tip of the single-use container to their eye or to any surface, in order to avoid eye injury or contamination of the solution.

Use With Contact Lenses

Advise patients that contact lenses should be removed prior to administration of Xiidra and can be reinserted 15 minutes after administration *[see Dosage and Administration (2)]*.

Administration

Advise patients that the solution from one single-use container is to be used immediately after opening. It can be used to dose both eyes. The single-use container, including any remaining contents should be discarded immediately after administration *[see Dosage and Administration (2)]*.

Storage Information

Instruct patients to store single-use containers in the original foil pouch until ready to use *[see How Supplied/Storage and Handling (16)]*.

Distributed by:

Bausch & Lomb Americas Inc., Bridgewater, NJ 08807 USA

Patented. See <https://patents.bausch.com> for US patent information.

Xiidra is a trademark of Bausch & Lomb Incorporated or its affiliates.

© 2023 Bausch & Lomb Incorporated or its affiliates

9800800

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use MIEBO safely and effectively. See full prescribing information for MIEBO.

MIEBO™ (perfluorohexyloctane ophthalmic solution), for topical ophthalmic use
Initial U.S. Approval: 2023

INDICATIONS AND USAGE

MIEBO (perfluorohexyloctane ophthalmic solution) is a semifluorinated alkane indicated for treatment of the signs and symptoms of dry eye disease. (1)

DOSAGE AND ADMINISTRATION

Instill one drop of MIEBO four times daily into each eye. (2.1)

DOSAGE FORMS AND STRENGTHS

Ophthalmic solution: 100% perfluorohexyloctane. (3)

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Recommended Dosage
- 2.2 Administration Instructions

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Use with Contact Lenses

6 ADVERSE REACTIONS

- 6.1 Clinical Trials Experience

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy

- 8.2 Lactation

- 8.4 Pediatric Use

- 8.5 Geriatric Use

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action

- 12.3 Pharmacokinetics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

MIEBO™ (perfluorohexyloctane ophthalmic solution) is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

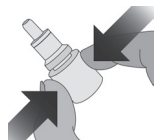
Instill one drop of MIEBO four times daily into affected eye(s).

Contact lenses should be removed prior to and for at least 30 minutes after the administration of MIEBO.

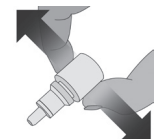
2.2 Administration Instructions

Step 1. Remove the cap from eye drop bottle.

Step 2. Holding the bottle upright, gently squeeze the bottle.



Step 3. While squeezing, turn the bottle upside down and release the pressure (drawing air into the bottle).



Step 4. Keeping the bottle upside down, place the bottle above your eye and squeeze it again to release a drop into your eye.



Repeat steps 1 - 4 for the second affected eye.

3 DOSAGE FORMS AND STRENGTHS

MIEBO (perfluorohexyloctane ophthalmic solution) is a sterile, clear and colorless ophthalmic solution containing 100% perfluorohexyloctane.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Use with Contact Lenses

MIEBO 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 MIEBO.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In patients with DED, 614 patients received at least one dose of MIEBO in two randomized controlled clinical trials across 68 sites in the United States. The most common ocular adverse reaction was blurred vision. Blurred vision and conjunctival redness were reported in 1-3% of individuals.

CONTRAINDICATIONS

None. (4)

ADVERSE REACTIONS

Most common ocular adverse reaction was blurred vision. Blurred vision was reported in less than 4% of individuals. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Bausch & Lomb Incorporated at 1-800-553-5340 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 5/2023

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well controlled studies with MIEBO in pregnant women.

In animal reproduction studies with oral administration of perfluorohexyloctane during the period of organogenesis, no adverse maternal or developmental effects were observed in rats at doses up to 162 times the recommended human ophthalmic dose (RHOD) (*see Data*). Maternal toxicity, miscarriages and reduced fetal weights were observed in rabbits at all doses tested, with the lowest dose as 41 times the RHOD.

All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the US general population, the estimated background risk of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies.

Data

Animal Data

An embryofetal study was conducted in pregnant rabbits administered perfluorohexyloctane by oral gavage on gestation days 6 to 19, to target the period of organogenesis. Perfluorohexyloctane produced maternal toxicity, characterized by reduced body weight gain and food consumption, and miscarriages at all doses tested, with the lowest dose as ≥ 250 mg/kg/day (41 times the RHOD based on body surface area). Reduced fetal weights were also observed at ≥ 250 mg/kg/day but no fetal mortality or malformations. A no observed adverse effect level (NOAEL) for maternal toxicity was not established in rabbits.

An embryofetal study was conducted in pregnant rats administered perfluorohexyloctane by oral gavage on gestation days 6 to 17, to target the period of organogenesis. There was no evidence of embryofetal toxicity or teratogenicity at doses up to 2,000 mg/kg/day (162 times the RHOD).

8.2 Lactation

There are no data on the presence of perfluorohexyloctane in human milk, the effects on the breastfed infant, or the effects on milk production. The lack of clinical data during lactation precludes a clear determination of the risk of MIEBO to an infant during lactation; however, the developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for MIEBO.

8.4 Pediatric Use

The safety and effectiveness of MIEBO in pediatric patients below the age of 18 years have not been established.

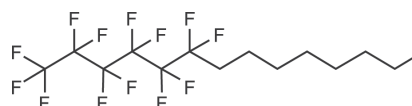
8.5 Geriatric Use

No overall differences in safety and effectiveness have been observed between elderly and younger patients.

11 DESCRIPTION

MIEBO™ (perfluorohexyloctane ophthalmic solution) is a sterile, clear and colorless liquid containing 100% perfluorohexyloctane, for topical ophthalmic use.

The active ingredient is 1,1,1,2,2,3,3,4,4,5,5,6,6-tridecafluorotetradecane and is a semifluorinated alkane. It has a molecular formula of $C_{14}H_{17}F_{13}$ and a molecular weight of 432.26 g/mol. The chemical structure is:



Perfluorohexyloctane is practically immiscible with water. It is miscible with ethanol and most organic solvents. Each multiple-dose bottle contains 3 mL of perfluorohexyloctane, 1.338 g/mL as a clear and colorless liquid.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Perfluorohexyloctane, a semifluorinated alkane, contains 6 perfluorinated carbon atoms and 8 hydrogenated carbon atoms. Perfluorohexyloctane forms a monolayer at the air-liquid interface of the tear film which can be expected to reduce evaporation. The exact mechanism of action for MIEBO in DED is not known.

12.3 Pharmacokinetics

The pharmacokinetics of perfluorohexyloctane following topical ocular administration of MIEBO has not been quantitatively characterized in humans. A single pharmacokinetic (PK) study was conducted that showed low systemic perfluorohexyloctane blood levels after topical ocular administration. Perfluorohexyloctane was not metabolized by human liver microsomes in vitro.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals have not been conducted to evaluate the carcinogenic potential of perfluorohexyloctane.

Perfluorohexyloctane was not mutagenic or clastogenic in a standard battery of genotoxicity tests, including a bacterial mutagenicity assay (Ames assay), an in vitro chromosome aberration assay using human peripheral lymphocytes, and an in vivo bone marrow micronucleus assay in rats.

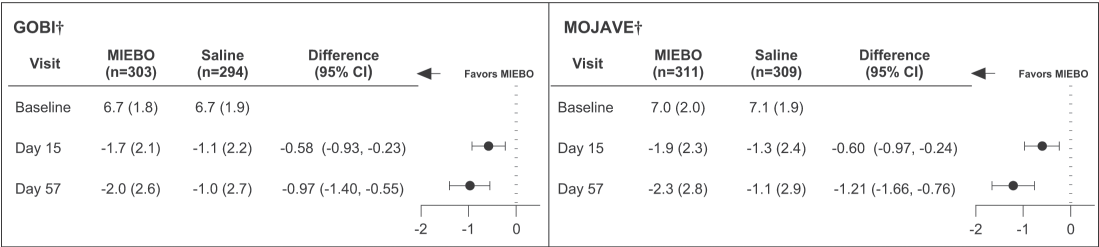
14 CLINICAL STUDIES

In two randomized, multicenter, double-masked, saline-controlled trials (GOBI and MOJAVE), a total of 1,217 patients with a history of DED and clinical signs of meibomian gland dysfunction were randomized to MIEBO or saline 0.6% (1:1 ratio) to evaluate safety and efficacy after receiving MIEBO four times daily (QID) for 57 days. The mean age of the 614 patients who received MIEBO was 57 years (range, 19-87 years). The majority of patients were female (76%).

Effects on Signs of Dry Eye Disease

Total corneal fluorescein staining (tCFS) was recorded at each study visit using a standardized grading system of 0-3 for each of the five areas on the cornea (inferior, superior, central, nasal, and temporal), totaling a maximum tCFS score for each eye of 15. The average baseline tCFS was approximately 6.7 in GOBI and 7.0 in MOJAVE. At Days 15 and 57, a statistically significant reduction in tCFS favoring MIEBO was observed in both studies (Figure 1).

Figure 1: Mean Change (Standard Deviation) from Baseline and Treatment Difference (MIEBO-Saline) in Total Corneal Fluorescein Staining (Study Eye) in 8-Week Study in Patients with Dry Eye Disease

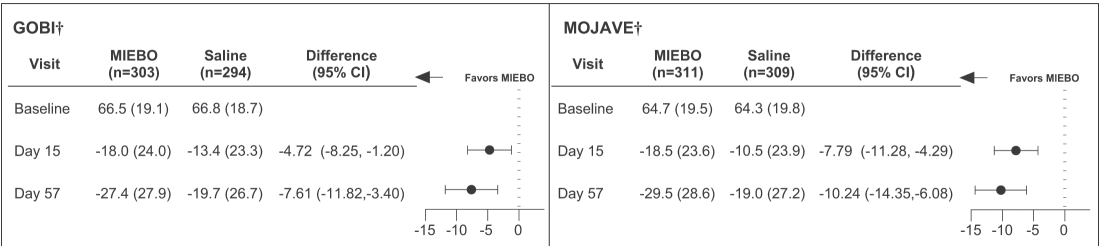


† A Phase 3, Multi-Center, Randomized, Double-Masked, Saline-Controlled Trial to Evaluate the Effect of NOV03 (Perfluorohexyloctane) on Signs and Symptoms of Dry Eye Disease Associated with Meibomian Gland Dysfunction

Effects on Symptoms of Dry Eye Disease

Eye dryness score was rated by patients using a visual analogue scale (VAS) (0=no discomfort, 100=maximal discomfort) at each study visit. The baseline VAS eye dryness average score was approximately 67 in GOBI and 65 in MOJAVE. At Days 15 and 57, a statistically significant reduction in VAS eye dryness score favoring MIEBO was observed in both studies (Figure 2).

Figure 2: Mean Change (Standard Deviation) from Baseline and Treatment Difference (MIEBO-Saline) in Eye Dryness Score (Study Eye) in 8-Week Study in Patients with Dry Eye Disease



† A Phase 3, Multi-Center, Randomized, Double-Masked, Saline-Controlled Trial to Evaluate the Effect of NOV03 (Perfluorohexyloctane) on Signs and Symptoms of Dry Eye Disease Associated with Meibomian Gland Dysfunction

16 HOW SUPPLIED/STORAGE AND HANDLING

MIEBO™ (perfluorohexyloctane ophthalmic solution) is supplied as a sterile, clear and colorless liquid in multiple-dose 5 mL polypropylene bottles with dropper tips and screw caps, packaged in a carton - NDC 24208-377-05.

Storage

Store MIEBO at 15°C to 25°C (59°F to 77°F). After opening, MIEBO can be used until the expiration date on the bottle.

17 PATIENT COUNSELING INFORMATION

Use with Contact Lenses

Advise patients that contact lenses should be removed prior to and for at least 30 minutes after administration of MIEBO.

Administration Instructions

Advise patients to instill one drop of MIEBO four times daily into each eye as depicted in the Administration Instructions [see Dosage and Administration (2.2)].

Distributed by:

Bausch & Lomb Americas Inc.
Bridgewater, NJ 08807 USA

Patented. See <https://patents.bausch.com> for US patent information.

MIEBO is a trademark of Bausch & Lomb Incorporated or its affiliates.

© 2023 Bausch & Lomb Incorporated or its affiliates

REF-MBO-0025