

Unlocking the Power of XDEMVMY[®] in Treating *Demodex* Blepharitis



Diagnosing *Demodex* blepharitis and examining pivotal SATURN data, and the ERSA and RHEA pilot studies.

BY RAVI PATEL, MD, MBA

Demodex blepharitis (DB)—inflammation caused by overpopulation of *Demodex* mites in the eyelash follicles—is particularly common and dramatically underdiagnosed.¹ It's estimated that approximately 25 million eye care patients in the United States are affected by DB.² This includes patients with cataracts, meibomian gland dysfunction (MGD), dry eye disease (DED), glaucoma, and other comorbidities, as well as soft contact lens wearers. In fact, 93% of patients (26 out of 28 patients) with intolerance to soft contact lens wear were found to have evi-

dence of *Demodex*.³ After demonstrating safety and tolerability, XDEMVMY[®] (lotilaner ophthalmic solution 0.25%; Tarsus), the first and only available FDA-approved treatment for DB, received its approval in August 2023. Here, I will discuss how to deliver an informed diagnosis of DB to patients and detail the efficacy and safety data from the SATURN studies that led to the approval of XDEMVMY[®].

DB DIAGNOSTIC CRITERIA AND PATIENT COMMUNICATION

There are multiple diagnostic criteria for DB, but I look for three specific

signs. First, inflammation produced by *Demodex* mites generates a chemical reaction that can cause hyperemia and telangiectasias of the vessels, which may lead to discomfort for patients. Second, these mites can cause damage to the shaft of the eyelashes. And, many patients may begin to experience loss of their eyelashes and other related issues. Overall, *Demodex* mites can cause inflammation of the eyelids, producing red, itchy, irritated eyelids, surface irritation, eyelash misdirection, eyelash loss, and fluctuating vision.

My diagnosis procedure includes examination for mild to severe DB. I have patients sit at the slit lamp, look down, and I check the lash line for collarettes. Collarettes are a pathognomonic sign for DB, and that's when I know to treat. I also make sure to evaluate all my MGD patients for DB.

When relaying my diagnosis to patients, I don't skirt around it; I tell them they have mites. However, it's important to reassure patients this is not a transmissible, contagious disease, and that millions of people have experienced this condition. Leading with this narrative is not only helpful to encourage patients to begin treatment, but it will also help reduce chair time to ensure the conversation is productive and focused on corrective treatment.

Collarettes reduced, mites eradicated, erythema cured¹

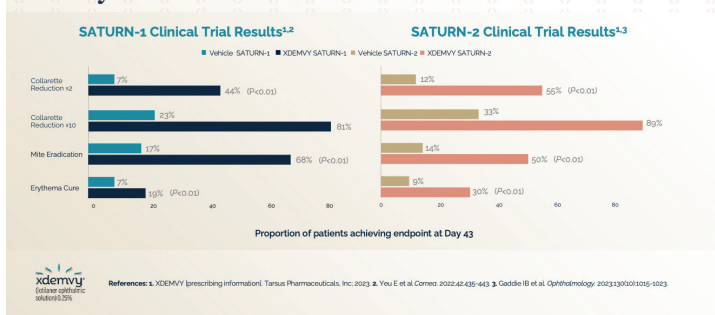


Figure 1. Efficacy endpoint results were similar between both SATURN trials.

XDEMVMY is tough on mites, easy on patients^{1,2}

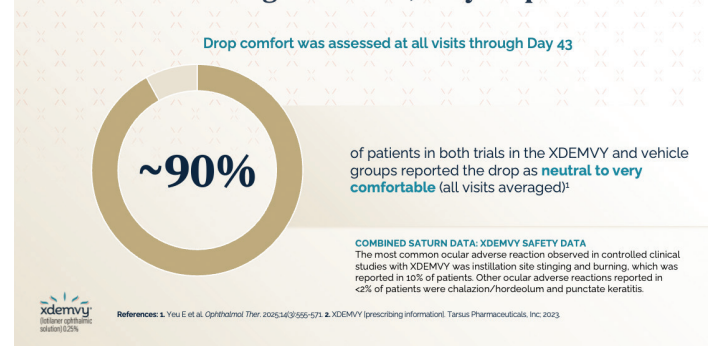


Figure 2. In the SATURN-1 and SATURN-2 trials, most patients found XDEMVMY[®] to be neutral to very comfortable.

INDICATIONS AND USAGE

XDEMVMY is indicated for the treatment of *Demodex* blepharitis.

Important Safety Information:

WARNINGS AND PRECAUTIONS

Risk of Contamination: Do not allow the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any

other surface in order to minimize contamination of the solution. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Use with Contact Lenses: XDEMVMY contains potassium sorbate, which may discolor soft contact lenses. Contact lenses should be removed prior to instillation of XDEMVMY and may be reinserted 15 minutes following its administration.

ADVERSE REACTIONS: The most common adverse reaction with XDEMVMY was instillation site stinging and burning which was reported in 10% of patients. Other ocular adverse reactions reported in less than 2% of patients were chalazion/hordeolum and punctate keratitis.

Please see Brief Summary of Prescribing Information on page 3.

SATURN TRIALS: XDEMVY® EFFICACY OUTCOMES

As of late 2023, we now have an FDA-approved treatment for DB. Lotilaner, the active ingredient in XDEMVY®, is a lipophilic agent in an aqueous drop that acts specifically via mite gamma-aminobutyric acid-gated (GABA-gated) chloride channels to target, paralyze, and kill *Demodex* mites.⁴⁻⁶ This treatment demonstrated its clinical efficacy and safety within 6 weeks in two clinical trials—SATURN-1 (phase 2b/3) and SATURN-2 (phase 3)—to receive FDA approval. Both trials examined the safety and efficacy of lotilaner ophthalmic solution 0.25% compared with vehicle for the treatment of *Demodex* blepharitis. The results between the two trials were similar, with reduced evidence of collarettes and the eradication of mites and erythema (Figure 1).

Fifty percent of patients in the studies achieved a collarette Grade 0 at day 43. Both studies demonstrated that 81% to 89% of patients had collarette reduction to less than 10, meaning four out of five patients achieved grade 1 or better in the 6 weeks of use timeframe, which is remarkable.^{6,7} Additionally, erythema was cured in about 25% of patients between the SATURN-1 and SATURN-2 trials. The recommended dosage is one drop per eye, twice a day, approximately 12 hours apart, over 6 weeks.⁴ The most common adverse reaction with XDEMVY® was instillation site stinging and burning which was reported in 10% of patients.⁴ Other ocular adverse reactions reported in less than 2% of patients included chalazion/hordeolum and punctate keratitis.⁴

In addition to the efficacy of lotilaner in its clinical trials, patients reported that it was comfortable to use. In fact, a tagline I often use for this treatment is: “XDEMVY® is tough on mites and easy on patients.” In the SATURN-1 and SATURN-2 trials, drop comfort was assessed at all visits up to day 43, and most patients in the trial found the drop to be neutral to very comfortable (averaging the responses for the 6-week

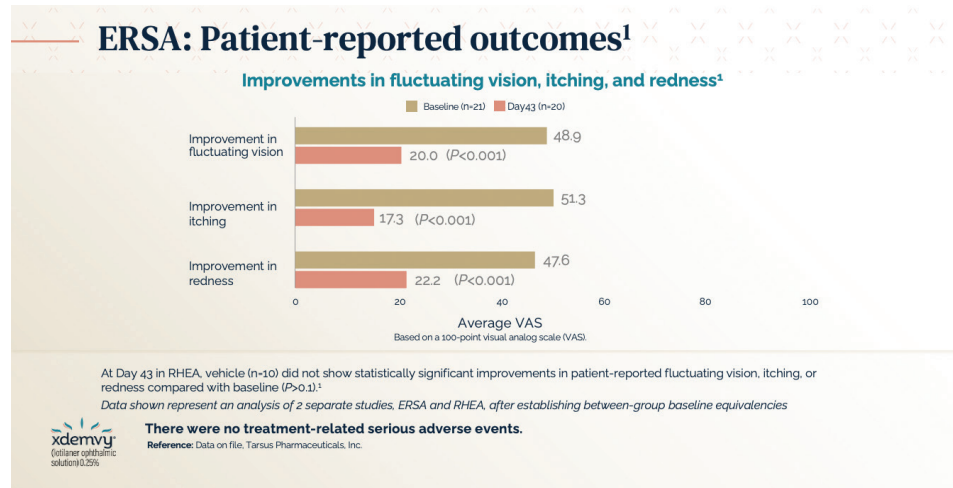


Figure 3. Patient-reported outcomes from the ERSA trial showed improvement in fluctuating vision, itching, and redness.

period) (Figure 2).^{6,7} In conclusion, lotilaner ophthalmic solution 0.25% proved to be a safe and effective treatment for patients with *Demodex* blepharitis.

ERSA & RHEA: DB AND MEIBOMIAN GLAND DISEASE TRIAL DATA

In addition to the SATURN trials, two separate pilot studies were conducted—ERSA and RHEA—in DB patients with MGD as well. These two studies were separate, randomized pilot trials with 21 patients enrolled in ERSA and 12 patients enrolled in RHEA, designed to explore the safety and efficacy of XDEMVY® in this specific patient population.⁸ Both trials had similar eligibility criteria and study endpoints of safety/tolerability, patient reported outcomes, collarette grade reduction, and meibomian gland function/expressibility. Participants had to have MGD and mite infestation in the same eye. They had to have at least 11 eyelashes with collarettes, otherwise known as grade 2, 3, or 4. Patients also needed to have at least one mite present based on epilated lashes from the upper and lower eyelids.

An initial question raised in these studies was how to measure MGD, and the determination was with meibomian glands yielding any liquid secretions (MGYLS). Overall, 15

meibomian glands were expressed in the lower eyelid and the secretions graded. For example, MGYLS means the patient had cloudy or clear liquid expressed from a gland that reflected a score of 2 and 3 respectively. A score of 0 meant no expression, and a score of 1 was solid expression. A meibomian gland secretion score of between 12 and 32 indicated MGD. Additionally, patients had to have at least grade-1 erythema, a tear breakup time of less than 10 seconds, and at least one-third of their meibomian glands had to be intact in this assessment.

At baseline in the ERSA study, 21 eyes of 21 patients had a mean of 7 expressible glands yielding any liquid secretion. At the end of 6 weeks, 10.8 out of 15 glands per 20 eyes of 20 patients (1 dropped out) yielded any liquid secretions, which is a 54% improvement in MGYLS.⁸ Furthermore, the ERSA trial results demonstrated that about 55% of patients had a reduction in collarettes to grade zero at the end of 6 weeks. Patients reported an improvement in fluctuating vision, itching, and redness when compared to baseline (Figure 3). At Day 43 in the RHEA study, the vehicle group did not show statistically significant improvement in mean collarette grade or in number of glands yielding any liquid secretion when

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Use with Contact Lenses: XDEMVY contains potassium sorbate, which may discolor soft contact lenses. Contact lenses should be removed prior to instillation of XDEMVY and may be reinserted 15 minutes following its administration.

ADVERSE REACTIONS: The most common adverse reaction with XDEMVY was instillation site stinging and burning which was reported in 10% of patients. Other ocular adverse reactions reported in less than 2% of patients were chalazion/hordeolum and punctate keratitis.

Please see Brief Summary of Prescribing Information on page 3.

compared to baseline. During this same period, the vehicle cohort also did not demonstrate statistically significant improvements in patient-reported fluctuating vision, itching, or redness when compared with baseline ($P > 0.1$).⁸

CONCLUSION

In my opinion, XDEMVY® is a great option for our DB patients, and as the data demonstrate, it works. The drops are tolerable and have no contraindications. If patients are contact lens wearers, I recommend that they wait 15 minutes after instilling the drop before putting the lenses back in the eyes.

For me, XDEMVY® works: I see collarettes and I prescribe it. In the beginning, I would have patients return for re-evaluation in 2-3 weeks to ensure they are on the right track and are tolerating it well. At this point, my confidence in the treatment is strong, and I prescribe it and ask the patient to contact us if they are experiencing any issues. Over the 6-week treatment course, I have been impressed in the efficacy of the medication, it matches that which we learned in the clinical trials. I encourage full treatment to ensure we are doing our best to eradicate the mites. Outside of drop instillation-related transient stinging and burning, patients are quite thrilled with the results. In the event of a recurrence in infestation, I am confident in prescribing XDEMVY. ■

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2. O'Dell L, Dierker DS, Devries DK, et al. Psychosocial impact of demodex blepharitis. *Clin Ophthalmol*. 2022;16:2979-2987.
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RAVI PATEL, MD, MBA

- Cornea and refractive specialist at Atlantic Eye in Eatontown, New Jersey
- Cornea service at Wills Eye Hospital in Philadelphia, Pennsylvania
- RPatel@atlanticeye.com
- Financial disclosure: Paid Consultant for Tarsus Pharmaceuticals, Inc.

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XDEMVY® (lotilaner ophthalmic solution) 0.25%, for topical ophthalmic use

BRIEF SUMMARY OF PRESCRIBING INFORMATION
Please see the XDEMVY® package insert for full Prescribing Information.

INDICATIONS AND USAGE

XDEMVY is indicated for the treatment of Demodex blepharitis.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Risk of Contamination Do not allow the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to minimize contamination of the solution. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

Use with Contact Lenses Contact lenses should be removed prior to instillation of XDEMVY and may be reinserted 15 minutes following its administration.

ADVERSE REACTIONS

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the 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.

XDEMVY was evaluated in 833 patients with Demodex blepharitis in two randomized, double-masked, vehicle-controlled studies (Saturn-1 and Saturn-2) with 42 days of treatment. The most common ocular adverse reaction observed in controlled clinical studies with XDEMVY was instillation site stinging and burning which was reported in 10% of patients. Other ocular adverse reactions reported in less than 2% of patients were chalazion/hordeolum and punctate keratitis.

USE IN SPECIFIC POPULATIONS

Pregnancy: Risk Summary There are no available data on XDEMVY use in pregnant women to inform any drug associated risk; however, systemic exposure to lotilaner from ocular administration is low. In animal reproduction studies, lotilaner did not produce malformations at clinically relevant doses.

Data Animal Data In an oral embryofetal developmental study in pregnant rats dosed during organogenesis from gestation days 6-19, increased post-implantation loss, reduced fetal pup weight, and incomplete skeletal ossification were observed at 50 mg/kg/day (approximately 1390 times the recommended human ophthalmic dose (RHOD) on a body surface area basis) in the presence of maternal toxicity (i.e., decreased body weight and food consumption). A rare malformation of situs inversus of the thoracic and abdominal viscera occurred in 1 fetus from a pregnant rat receiving 50 mg/kg/day; whether this finding was treatment-related could not be excluded. No maternal or embryofetal toxicity was observed at 18 mg/kg/day (approximately 501 times the RHOD on a body surface area basis). In an oral embryofetal development study in pregnant rabbits dosed during organogenesis from gestation days 7-19, no embryofetal toxicity or teratogenic findings were observed at 20 mg/kg/day (approximately 580-times the RHOD on an AUC basis), even in the presence of maternal toxicity (i.e., decreased food consumption and body weight).

In an oral two-generation reproductive toxicity study, F0 male and female rats were administered lotilaner at doses up to 40 mg/kg/day for 10 weeks before pairing and during the 2-week pairing period (3 weeks for males). Dosing for F0 females continued through lactation day 22. F1 male and female rats were administered lotilaner at 1 and 5 mg/kg/day post-weaning from day 23 for 10 weeks before pairing and during the 2-week pairing period (3 weeks for males). Dosing for F1 parental females continued through lactation day 22. There were no clear adverse effects on the F1 generation, and a slightly lower mean body weight during lactation was noted for F2 pups at 5 mg/kg/day. The no observed adverse effect level (NOAEL) was determined to be 5 mg/kg/day (approximately 139 times the RHOD on a body surface area basis).

Lactation: Risk Summary There are no data on the presence of XDEMVY in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lotilaner following 6 weeks of topical ocular administration is low and is >99% plasma protein bound, thus it is not known whether measurable levels of lotilaner would be present in maternal milk following topical ocular administration. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for XDEMVY and any potential adverse effects on the breast-fed child from XDEMVY.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

Geriatric Use: No overall differences in safety or effectiveness have been observed between elderly and other adult patients.

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis Long-term studies in animals have not been performed to evaluate the carcinogenic potential of lotilaner.

Mutagenesis Lotilaner was not genotoxic in the following assays: Ames assay for bacterial gene mutation, *in vitro* chromosomal aberration assay in cultured human peripheral blood lymphocytes, and *in vivo* rat micronucleus test.

Impairment of fertility In a two-generation study of reproductive performance in rats, F0 male and female rats were administered lotilaner at oral doses of 40 mg/kg/day for 80 days reduced to 20 mg/kg/day for 47-50 supplementary days. Reduced pregnancy rates and decreased implantation rates were observed in F0 females at doses 20 mg/kg/day (approximately 556 times the RHOD on a body surface area basis), which were also associated with maternal toxicity (i.e., decreased body weight and food consumption). No effects on fertility were observed in F0 females at the dose of 5 mg/kg/day (approximately 139 times the RHOD on a body surface area basis). No effects on fertility were observed in F0 males at the oral dose of 20 mg/kg/day (approximately 556 times the RHOD on a body surface area basis), and no effects on fertility were observed in F1 males and females at the oral dose of 5 mg/kg/day (approximately 139 times the RHOD on a body surface area basis).

PATIENT COUNSELING INFORMATION

Handling the Container Instruct patients to avoid allowing the tip of the dispensing container to contact the eye, surrounding structures, fingers, or any other surface in order to minimize contamination of the solution. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions.

When to Seek Physician Advice Advise patients that if they develop an intercurrent ocular condition (e.g., trauma or infection), have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of XDEMVY.

Use with Contact Lenses Advise patients that XDEMVY contains potassium sorbate, which may discolor soft contact lenses. Contact lenses should be removed prior to instillation of XDEMVY and may be reinserted 15 minutes following its administration.

Use with Other Ophthalmic Drugs Advise patients that if more than one topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes between applications.

Missed Dose Advise patients that if one dose is missed, treatment should continue with the next dose.

Available by prescription only.

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