

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

XDEMVY™ (lotilaner ophthalmic solution) 0.25%, for topical ophthalmic use
Initial U.S. Approval: 2023

-----**INDICATIONS AND USAGE**-----

XDEMVY is an ectoparasiticide (anti-parasitic) indicated for the treatment of Demodex blepharitis. (1)

-----**DOSAGE AND ADMINISTRATION**-----

Instill one drop of XDEMVY in each eye twice daily (approximately 12 hours apart) for 6 weeks. (2)

-----**DOSAGE FORMS AND STRENGTHS**-----

Ophthalmic solution containing lotilaner 0.25%. (3)

-----**CONTRAINDICATIONS**-----

None. (4)

-----**ADVERSE REACTIONS**-----

The most common adverse reaction was instillation site stinging and burning (10%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Tarsus Pharmaceuticals at 1-888-421-4002 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 7/2023

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

XDEMVY is indicated for the treatment of Demodex blepharitis.

2 DOSAGE AND ADMINISTRATION

Instill one drop of XDEMVY in each eye twice daily (approximately 12 hours apart) for 6 weeks. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart. If one dose is missed, treatment should continue with the next scheduled dose.

3 DOSAGE FORMS AND STRENGTHS

XDEMVY (lotilaner ophthalmic solution) is provided as an ophthalmic solution containing lotilaner 0.25% (2.5 mg/mL).

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 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.

5.2 Use with Contact Lenses

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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.

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on XDEMZY use in pregnant women to inform any drug associated risk; however, systemic exposure to lotilaner from ocular administration is low [see *Clinical Pharmacology (12.3)*]. 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 parenteral 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).

8.2 Lactation

Risk Summary

There are no data on the presence of XDEMZY 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 [see *Clinical Pharmacology (12.3)*], 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 XDEMZY and any potential adverse effects on the breast-fed child from XDEMZY.

8.4 Pediatric Use

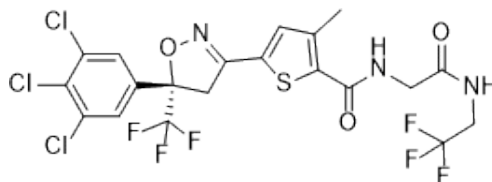
Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

8.5 Geriatric Use

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

11 DESCRIPTION

Lotilaner is a member of the isoxazoline family of compounds. Its chemical name is 2-Thiophenecarboxamide, 5-[(5S)-4,5-dihydro-5-(3,4,5-trichlorophenyl)-5-(trifluoromethyl)-3-isoxazolyl]-3-methyl-N-[2-oxo-2-[(2,2,2-trifluoroethyl)amino]ethyl]-2-thiophenecarboxamide. The molecular formula is $C_{20}H_{14}Cl_3F_6N_3O_3S$. The molecular weight is 596.76 g/mol. The chemical structure is:



XDEMZY is a sterile, preserved, multi-dose, slightly yellowish, slightly opalescent, topical ophthalmic solution containing lotilaner, 0.25% as the active ingredient. It is preserved with potassium sorbate and contains the following additional inactive ingredients: edetate disodium, hydroxypropyl methylcellulose (HPMC), polyoxyl 35 castor oil, glycerin, dibasic sodium phosphate, monobasic sodium phosphate, and water for injection.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Lotilaner is a gamma-aminobutyric acid (GABA)-gated chloride channel inhibitor selective for mites. Inhibition of these GABA chloride channels causes a paralytic action in the target organism leading to its death. Lotilaner is not an inhibitor of mammalian GABA mediated chloride channels when tested at up to 30 μ M (18 μ g/mL) *in vitro* (approximately 1100 times the RHOD).

12.3 Pharmacokinetics

The systemic pharmacokinetic profile after topical ocular administration was evaluated in healthy volunteers after single and repeat dose administration. The systemic exposure was evaluated in patients at the end of 6 weeks of treatment.

Absorption

Maximum lotilaner concentration was observed 2 hours after a single ocular administration on Day 1 and 1 hour after the last drug administration on Day 42. In healthy subjects, the peak concentration (C_{max}) and total exposure (AUC_{0-12}) of lotilaner in whole blood increased after 42 days of repeated ocular administration from 0.596 to 17.8 ng/mL and from 5.75 to 149 hr•ng/mL for C_{max} and AUC_{0-12} respectively. The effective half-life of lotilaner, which is based on the accumulation ratio over the dosing interval of 12 hours, was 264 hours (11 days). In patients with Demodex blepharitis (n=138) who received XDEMY twice daily for 42 days, the mean (range) systemic exposure at the end of treatment was 12.0 ng/mL (0.4-46.1 ng/mL).

Distribution

Lotilaner plasma protein binding is high (> 99.9%) in human plasma. The partitioning of lotilaner to human blood cells is approximately 10% (range 0-20%).

Elimination

The effective half-life in healthy subjects, which is based on the accumulation ratio over the dosing interval of 12 hours, is 264 hours (11 days).

Metabolism

Lotilaner is not metabolized by CYP enzymes.

13 NONCLINICAL TOXICOLOGY

13.1 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

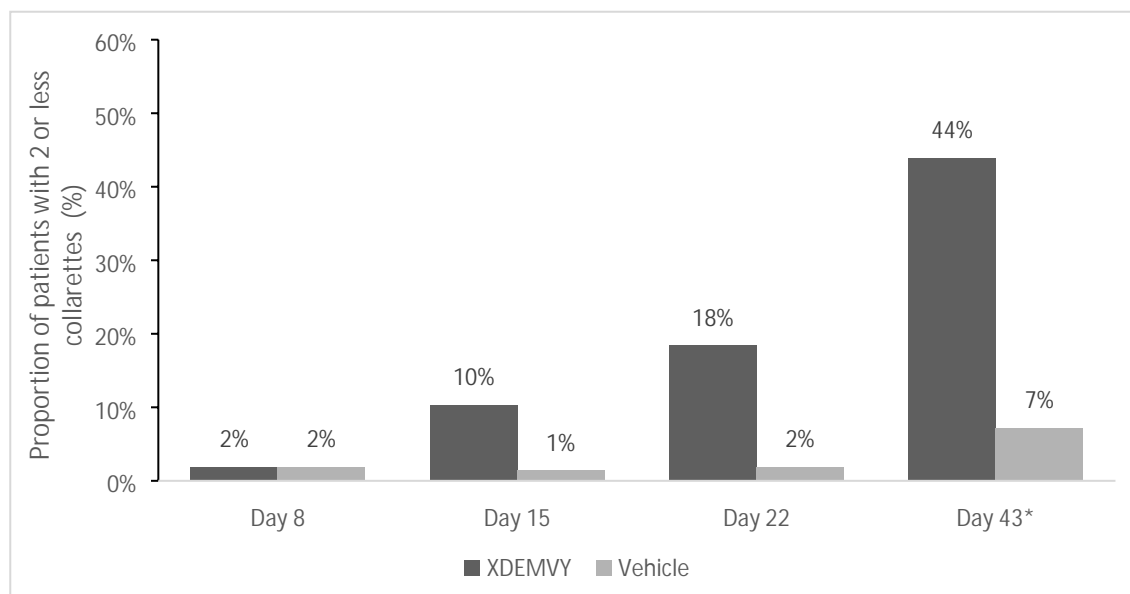
implantation rates were observed in F0 females at doses 20 mg/kg/day) (approximately 556 times the RHOD on a body surface area basis), which were also associated with maternal toxicity (i.e., decreased body weight and food consumption). No effects on fertility were observed in F0 females at the dose of 5 mg/kg/day (approximately 139 times the MRHOD 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).

14 CLINICAL STUDIES

The safety and efficacy of XDEMZY for the treatment of Demodex blepharitis was evaluated in a total of 833 patients (415 of which received XDEMZY) in two 6-week, randomized, multicenter, double-masked, vehicle-controlled studies (Saturn-1 and Saturn-2). Patients with Demodex blepharitis were randomized to either XDEMZY or Vehicle at a 1:1 ratio dosed twice daily in each eye.

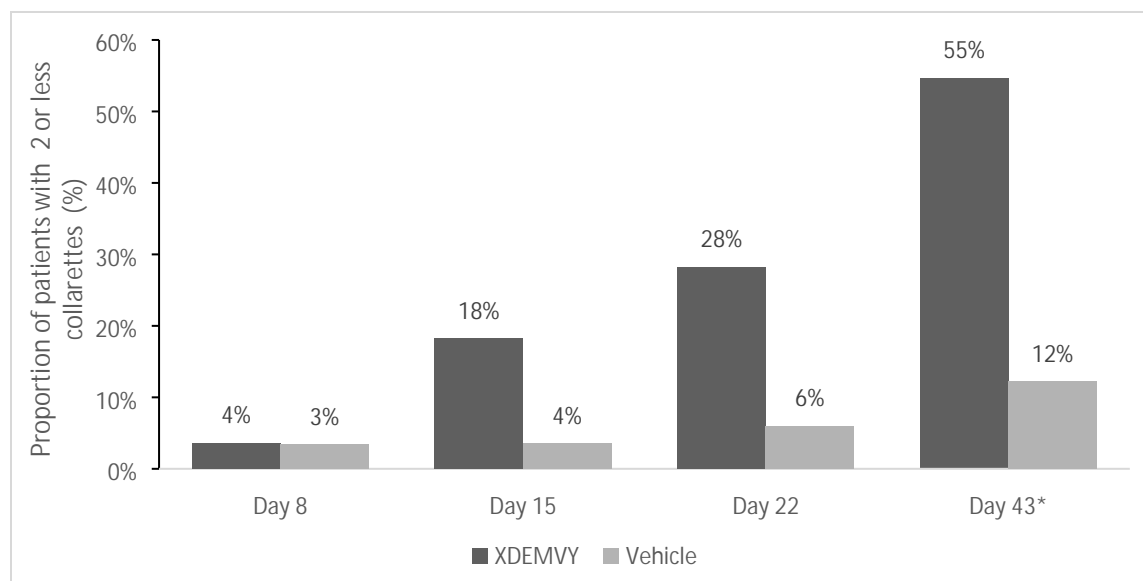
Efficacy was demonstrated by improvement in lids (reduction of collarettes to no more than 2 collarettes per upper lid) in each study (Saturn-1 and Saturn-2) (see Figure 1 and Figure 2) by Day 43.

Figure 1. Saturn-1: Proportion of patients with 2 or less collarettes for the upper eyelid



*Day 43 Primary Endpoint; XDEMZY N=209, Vehicle N=204, p-value <0.01

Figure 2. Saturn-2: Proportion of patients with 2 or less collarettes for the upper eyelid



*Day 43 Primary Endpoint; XDEM VY N=193, Vehicle N=200, p-value <0.01

The endpoints of mite eradication (mite density of 0 mites/lash) and erythema cure (Grade 0) of XDEM VY vs. Vehicle demonstrated statistically significant improvement at Day 43 across both Saturn-1 (Table 1) and Saturn-2 (Table 2) studies.

Table 1: Proportion of patients with eradication of Demodex mites and erythema cure in the analysis eye at Day 43 in Saturn-1

	XDEM VY (N=212)	Vehicle (N=209)	p-value
Mite Eradication	68%	17%	< 0.01
Erythema Cure	19%	7%	< 0.01

Table 2: Proportion of patients with eradication of Demodex mites and erythema cure in the analysis eye at Day 43 in Saturn-2

	XDEM VY (N=203)	Vehicle (N=209)	p-value
Mite Eradication	50%	14%	< 0.01
Erythema Cure	30%	9%	< 0.01

16 HOW SUPPLIED/STORAGE AND HANDLING

XDEMZY is supplied as a sterile ophthalmic solution in a white, opaque, low-density polyethylene (LDPE) multiple-dose bottle with a LDPE dropper tip and tan high-density polyethylene (HDPE) cap.

10 mL fill in a 11 mL container	NDC # 81942-125-01
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Storage

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

17 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 XDEMZY.

Use with Contact Lenses

Advise patients that XDEMZY contains potassium sorbate, which may discolor soft contact lenses. Contact lenses should be removed prior to instillation of XDEMZY 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.

XDEMYY and/or methods of use thereof may be covered by one or more of the patents listed at www.tarsusrx.com/patents

XDEMYY is a trademark of Tarsus Pharmaceuticals, Inc.

Manufactured for: Tarsus Pharmaceuticals, Inc., Irvine, CA 92618