CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

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

Application Type	NDA
Application Number	217603
PDUFA Goal Date	August 25, 2023
Nexus TTT #	2022-1048
Reviewer Name(s)	Carla Darling, Pharm.D., BCPS
Team Leader	Jacqueline Sheppard, Pharm.D.
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	June 15, 2023
Subject	Evaluation of Need for a REMS
Established Name	Lotilaner
Trade Name	Xdemvy
Name of Applicant	Tarsus Pharmaceuticals, Inc.
Therapeutic Class	Isoxazoline
Formulation(s)	Lotilaner ophthalmic solution, 0.25%
Dosing Regimen	Instill one drop twice daily into each eye for 6 weeks

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EXECUTIVE SUMMARY

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity Xdemvy (lotilaner) is necessary to ensure the benefits outweigh its risks. Tarsus Pharmaceuticals, Incorporated (Applicant) submitted a New Drug Application (NDA) 217603 for lotilaner with the proposed indication for the treatment of Demodex blepharitis. The risks associated with lotilaner include instillation site stinging and burning. The applicant did not submit a proposed REMS or risk management plan with this application.

DRM and the Division of Ophthalmology agree that a REMS is not needed to ensure the benefits of lotilaner outweigh its risks. The two pivotal, vehicle-controlled phase 2b/3 and 3 studies demonstrated the benefit of lotilaner in the treatment of Demodex blepharitis that is statistically superior to vehicle in collarette elimination (collarette score = 0). The main risk associated with lotilaner includes instillation site stinging and burning. This risk is included in the adverse reactions section of the labeling. The health care providers likely to prescribe lotilaner should be familiar with monitoring and management of this risk. Based on the safety and efficacy demonstrated in clinical trials, the benefit-risk profile is acceptable and risk mitigation beyond labeling is not required.

1. Introduction

This review by the Division of Risk Management (DRM) evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) Xdemvy (lotilaner) is necessary to ensure the benefits outweigh its risks. Tarsus Pharmaceuticals, Incorporated (Applicant) submitted a New Drug Application (NDA) 217603 for lotilaner with the proposed indication for Demodex blepharitis. This application is under review in the Division of Ophthalmology. The applicant did not submit a proposed REMS or risk management plan with this application.

2. Background

2.1. Product Information

Lotilaner, a new molecular entity (NME)[a], is an isoxazoline proposed for the treatment of Demodex blepharitis. The mechanism of action in Demodex blepharitis is to inhibit mite specific gamma-aminobutyric acid (GABA)-gated chloride channels that causes a paralytic action in mites leading to their death.[1] Lotilaner is not an inhibitor of human GABA chloride channels.[1,2] The proposed dosage regimen is to instill one drop into each eye twice daily for 6 weeks.[1,] [b] Lotilaner is intended for administration by patients or caregivers in the outpatient setting.

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

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

Oral lotilaner is FDA approved for the treatment and prevention of flea infestations and the treatment and control of tick infestations in dogs (2018) and cats (2021).[2,3] Oral lotilaner is also authorized for use as a veterinary medicine to treat flea and tick infestations in dogs and cats in the European Union (2017).[4] If approved, lotilaner will be the first drug approved for Demodex blepharitis.

2.2. Regulatory History

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

- 08/25/2022: NDA 217603 submission for the treatment of Demodex blepharitis received
- 01/31/2023: A mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that there were no major safety issues identified to date for lotilaner.

3. Therapeutic Context and Treatment Options

3.1. Description of the Medical Condition

Blepharitis is a common ocular disease characterized by inflammation of the eyelid margins and ocular irritation.[5] Blepharitis can be due to bacteria or Demodex among other etiologies.[5,6] Demodex mites are a natural pathogen found on human skin and two known species of Demodex have been confirmed to inhabit the human eyelid including Demodex folliculorum and Demodex brevis.[6,7] Demodex blepharitis can be asymptomatic or result in redness, itching and burning sensations.[7,8] If left untreated, Demodex blepharitis can lead to corneal complications including neovascularization, ulceration, trichiasis, and other changes in eyelid morphology.[6, c]

The prevalence of blepharitis in the United States (U.S.) is largely unknown, some estimate that approximately 25 million people are affected.[6] According to the Applicant, blepharitis is estimated to affect as many as 19 million Americans.[9] It is important to consider that not all of cases of blepharitis are associated with Demodex. In a recent U.S. study, 54% to 65% of patients seen by and ophthalmologist or optometrist had collarettes, the pathognomonic sign of Demodex blepharitis.[10, d]

3.2. Description of Current Treatment Options

Current treatment goals for blepharitis are to reduce signs and symptoms, minimize structural damage, and prevent loss of visual function.[11] There are no pharmacological Food and Drug Administration (FDA) approved treatments for Demodex blepharitis; therefore, there is an unmet medical need for an effective treatment. Off-label treatments include the use of topical tea tree oil (TTO), oral ivermectin

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

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

and metronidazole, and topical selenium sulfide. Studies show that topical TTO can be effective at reducing Demodex count with few reports of serious effects; however, TTO in high concentrations may be toxic to the eye and induce ocular irritation and allergic reactions.[6] Severe systemic reactions have been reported with oral ivermectin or metronidazole use including the Mazzotti reaction, fatal encephalopathy, and increased international normalized ratio with hemorrhage.[6,11]

Nonpharmacological treatment options for symptomatic management of Demodex blepharitis include, warm compresses, eyelid cleaning, and microblepharoexfoliation.[6,11]

4. Benefit Assessment

The efficacy and safety of lotilaner for the treatment of Demodex blepharitis is supported by two pivotal trials, a phase 2b/3 study, TRS-009 (NCT04475432) and a phase 3 study, TRS-010 (NCT04784091). Both studies were multicentered, randomized, double-masked, vehicle-controlled to evaluate the efficacy and safety of lotilaner in adults with Demodex blepharitis. A total of 833 patients (study TRS-009 and study TRS-010) were randomized 1:1 to receive one drop of lotilaner ophthalmic solution or vehicle ophthalmic solution, bilaterally, twice daily for 43 days (approximately 6 weeks). The primary endpoint was the proportion of patients cured based on a collarette score of 0 for the upper eyelid of the analysis eye at Day 43. The secondary efficacy endpoints included:

- Proportion of subjects with eradication of Demodex mites based on a mite density of 0 in the analysis eye at Day 43
- Proportion of subjects cured based on composite collarette and erythema scores of 0 for the upper eyelid of the analysis eye at Day 43 (referred to as a composite cure)

The review team determined that the two pivotal studies, study TRS-009 and TRS-010, support approval of lotilaner for the treatment of Demodex blepharitis. Lotilaner was statistically superior to vehicle in both studies by showing higher proportion of lotilaner treated patients achieving a cure (collarette score = 0) compared to vehicle at day 43. Table 1 highlights the results of the primary endpoints for both studies. Additionally, lotilaner shows statistical improvement in both secondary endpoints of mite eradication and composite score of collarette elimination and cure of eyelid erythema.

Table 1: Results of the Primary Efficacy Endpoints*

	Study TRS-009		**Study TSR-010**	
Proportion of Subjects Achieving a Cure	**Lotilaner** (n=212)	**Vehicle** (n=209)	**Lotilaner** (n=203)	**Vehicle** (n=209)
Cured (collarette score = 0), N (%) (SE)	93 (44%) (3.4)	15 (7%) (1.8)	111 (55%) (3.5)	25 (12%) (2.3)
Difference in proportion cured (SE)[a]	0.3669 (0.0386)		0.4250 (0.0422)	
p-value[b]	< 0.0001		< 0.0001	

*Modified from the Clinical Review as of March 20, 2023[12]
Abbreviations: SE=standard error
[a] The difference was computed as lotilaner ophthalmic solution minus vehicle.
[b] The p-value was from a difference of proportions test.

The clinical reviewer concluded that lotilaner demonstrated substantial evidence of effectiveness by showing clinically relevant and statistically significant evidence that lotilaner provides complete resolution of eyelash collarettes in Demodex blepharitis.[12, e]

5. Risk Assessment & Safe-Use Conditions

The safety database includes 415 patients exposed to at least one dose of lotilaner from two phase 3 studies, TRS-009 (n=212) and TRS -010 (n=203). Instillation site pain (10%) was the most commonly reported adverse event in ≥ 5% of participants receiving lotilaner compared to vehicle (7%).[f] No deaths occurred in the two pivotal clinical trials. Seven (7) patients treated with lotilaner had serious adverse reactions[g] (SAR) including diabetic retinopathy, gastrointestinal hemorrhage, intestinal obstruction, COVID-19, pneumonia, vascular access site pseudoaneurysm, bladder cancer, hematuria, uterine prolapse, dyspnea. Overall, the clinical reviewer concluded that none of the adverse events appear to be related to the treatment drug and that "no adverse safety signals or trends were observed based on a review of SAEs and other significant treatment emergent adverse events (TEAEs)."[12] Proposed labeling includes the risk of instillation site stinging and burning in Section 6, Adverse Events of the prescribing information.[1]

6. Expected Postmarket Use

Lotilaner is likely to be prescribed by primary care clinicians and eye care specialists and is expected to primarily be used by patients in the outpatient setting. If approved, lotilaner will be the first drug approved for Demodex blepharitis. Healthcare providers who are likely to prescribe lotilaner should be familiar with monitoring and management of this risk based on similar risk profile of other commonly prescribed approved ophthalmic products such as those for the treatment of dry eye disease.

7. Risk Management Activities Proposed by the Applicant

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

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

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

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

8. Discussion of Need for a REMS

The clinical reviewer recommends approval of lotilaner on the basis of the efficacy and safety information currently available.[12]

Lotilaner is an isoxazoline proposed for treatment Demodex blepharitis. Demodex blepharitis is a common ocular disease that can be asymptomatic or result in redness, itching and burning sensations. If left untreated, Demodex blepharitis can lead to corneal complications including neovascularization, ulceration, trichiasis, and other changes in eyelid morphology.

As there are no approved treatments designed cure the disease, there remains an unmet need for treatment options for Demodex blepharitis. Lotilaner offers an effective treatment option for Demodex blepharitis. The use of lotilaner resulted in a statistically superior to vehicle in achieving a cure (collarette score = 0) compared to vehicle at day 43. The Division of Ophthalmology determined that there is substantial evidence of effectiveness for lotilaner for the treatment of Demodex blepharitis with an acceptable safety profile.

Lotilaner is associated with a risk of instillation site stinging and burning. There were no reported ocular and non-ocular adverse events associated with lotilaner that were serious. As the risk of instillation site stinging and burning is not a serious safety risk, this reviewer concluded that based on the available safety information, a REMS is not necessary to ensure the benefits outweigh the risks.

9. Conclusion & Recommendations

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

Based on the clinical review, the benefit-risk profile is favorable therefore, a REMS is not necessary for lotilaner to ensure the benefits outweigh the risks. At the time of this review, evaluation of safety information and labeling was ongoing. Please notify DRM if new safety information becomes available that changes the benefit-risk profile; this recommendation can be reevaluated.

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

10. Appendices

10.1. References

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