Drug Monograph

Drug Name: **Tyrvaya™ (varenicline solution) nasal spray**
Drug Class: **Dry Eye Disease**
Prepared For: MO HealthNet
Prepared By: Conduent

☒ **New Criteria** ☐ **Revision of Existing Criteria**

Executive Summary

Purpose:	The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be made available on an open access basis to prescribers, require a clinical edit or require prior authorization for use.
Dosage Forms:	Tyrvaya is available in a carton containing two nasal spray amber glass bottles, each containing 60 sprays per bottle. Each spray delivers 0.03 mg varenicline per spray (0.05 mL).
Manufacturer:	Distributed by: Oyster Point Pharma, Inc., Princeton, NJ 08540
Summary of Findings:	Tyrvaya's efficacy was evaluated in two randomized, multicenter, double-masked, vehicle-controlled trials: ONSET-1 trial (n=182), and ONSET-2 trial (n=758). Patients were randomized to receive Tyrvaya, varying strengths of varenicline solutions that were not FDA approved, or vehicle. The primary efficacy endpoint for both studies reflected a measure of tear production targeting patients achieving a ≥ 10 mm improvement in Schirmer's score from baseline to Day 28. In each study, Tyrvaya produced a statistically significant improvement in the primary endpoint. In ONSET-1, 52% of patients receiving Tyrvaya versus 14% receiving vehicle (p<0.01) met the primary endpoint, and 47% receiving Tyrvaya versus 28% receiving vehicle (p<0.01) met the primary endpoint in ONSET-2.

Status Recommendation:	☐ Clinical Edit ☐ Open Access	☐ PA Required ☒ PDL
Type of PA Criteria:	☐ Appropriate Indications ☐ No PA Required	☒ Non-Preferred ☐ Preferred

Purpose

The purpose of this monograph is to provide a review of new therapy to determine whether the reviewed drug should be considered a prior authorization drug, a clinical edit drug or an open access drug. While prescription expenditures are increasing at double-digit rates, payers are evaluating ways to control these costs by influencing prescriber behavior and guide appropriate medication usage. This review will assist in the achievement of qualitative and economic goals related to health care resource utilization. Restricting the use of certain medications can reduce costs by requiring documentation of appropriate indications for use, and where appropriate, encourage the use of less expensive agents within a drug class.

Introduction [1]

Dry eye disease (DED), also known as keratoconjunctivitis sicca, dry eye syndrome, or dysfunctional tear syndrome, is characterized by disruption of the tear film, causing decreased tear production, rapid tear film evaporation, or instability of the tear film. This leads to ocular discomfort, irritation, blurriness or light sensitivity, and ocular surface inflammation. In the United States, the prevalence of physician-diagnosed dry eye or severe dry eye symptoms was 7.8% in women and 4.3% in men over age 50 based on data from the Women's Health Study and the Physician's Health Studies. Place of residence did not affect the prevalence of DED. Treatment for this syndrome is focused on reducing symptoms, maintaining visual function, and reducing or preventing ocular surface damage. First-line therapies are ocular lubricants. Prescription medications are available to treat the underlying causes of DED and include topical antibiotics or antibiotic/steroid combinations, short duration topical corticosteroids, topical secretagogues, topical cyclosporine, topical lymphocyte function associated antigen 1 (LFA-1) antagonist agents (lifitegrast), and oral antibiotics (macrolides or tetracyclines).

Dosage Form [2]

Tyrvaya is available in a carton containing two nasal spray amber glass bottles, each containing 60 sprays per bottle. Each spray delivers 0.03 mg varenicline per spray (0.05 mL). Each carton is equal to a 30-day supply.

Manufacturer [2]

Distributed by: Oyster Point Pharma, Inc., Princeton, NJ 08540

Indication(s) [2]

Tyrvaya is indicated for the treatment of the signs and symptoms of dry eye disease.

Clinical Efficacy [1,3,4,5] (mechanism of action/pharmacology, comparative efficacy)

Tyrvaya is a partial α4β2, α4α6β2, α3β4, α3α5β4, and full α7 neuronal nicotinic acetylcholine receptor agonist. It binds at the heteromeric sub-type(s) of the nicotinic acetylcholine receptor, causing agonist activity resulting in activation of the trigeminal parasympathetic pathway, causing an increase in basal tear film. The exact mechanism of action is unknown currently.

Pharmacokinetics:

Metabolism	Minimal
Half-life elimination	~19 ± 10 hours
Time to peak	≤ 2 hours
Excretion	Urine (92% as unchanged drug)

Clinical Trials Experience

STUDY DESIGN (NCT03636061 and NCT04036292)	Tyrvaya was studied in 2 randomized, multicenter, double-masked, vehicle-controlled trials: Phase 2 ONSET-1 trial (n=182), and Phase 3 ONSET-2 trial (n=758).	
INCLUSION CRITERIA	• ≥ 22 years old • Anesthetized Schirmer's test score* range: 1-10 mm • Corneal fluorescein staining range**: 2-14 • Used or desired to use artificial tear substitute for dry eye symptoms < 6 months prior to 1st visit	
EXCLUSION CRITERIA	• Any intraocular or extraocular surgery in either eye within 3 months, or refractive surgery within 12 months of 1st visit	
TREATMENT REGIMEN	**ONSET-1** Patients were randomized 1:1:1:1 to receive one spray in each nostril twice daily of one of the following: • 0.006 mg varenicline solution (n=47) • 0.03 mg Tyrvaya (n=48) • 0.06 mg varenicline solution (n=44) • Vehicle (n=43)	**ONSET-2** Patients were randomized 1:1:1 to receive one spray in each nostril twice daily of one of the following: • 0.03 mg Tyrvaya (n=260) • 0.06 mg varenicline solution (n=246) • Vehicle (n=252)

RESULTS

For ONSET-1, the primary endpoint was change in anesthetized Schirmer's test score (STS) from baseline to Day 28. Secondary outcomes included change from baseline in eye dryness score (EDS)*** from baseline to Day 28 and change in EDS from baseline to day 21 at 5 minutes post-treatment in controlled adverse environment (CAE).

For ONSET-2, the primary endpoint was the percentage of subjects who achieved ≥ 10 mm improvement in STS from baseline to Day 28. Secondary outcomes included change in anesthetized STS from baseline to Day 28, change in EDS from baseline to Day 28 (in clinic setting), and change in EDS from baseline to Day 28 at 5 minutes post-treatment in CAE.

Patients Achieving ≥ 10 mm Improvement from Baseline in STS at Day 28

	ONSET-1		**ONSET-2**	
	Tyrvaya (n=48)	**Vehicle (n=43)**	**Tyrvaya (n=260)**	**Vehicle (n=252)**
≥ 10 mm increase in tear production (% of eyes) at Day 28	52%	14%	47%	28%
Proportion difference (95% CI)	38% (21%, 56%)		20% (11%, 28%)	
p value vs. control	<0.01		<0.01	
Mean change in STS at Day 28	11.7 mm	3.2 mm	11.3 mm	6.3 mm

<table>
<tr><td></td><td>Change in EDS
<table>
<tr><td></td><td colspan="2">ONSET-1</td><td colspan="2">ONSET-2</td></tr>
<tr><td></td><td>Tyrvaya (n=45)</td><td>Vehicle (n=42)</td><td>Tyrvaya (n=187)</td><td>Vehicle (n=169)</td></tr>
<tr><td>Change from baseline in EDS at Day 21 (ONSET-1) or Day 28 (ONSET-2) in CAE</td><td>-16 mm</td><td>-4.4 mm</td><td>-10.3 mm</td><td>-7.4 mm</td></tr>
<tr><td>p value vs. control</td><td colspan="2"><0.01</td><td colspan="2">>0.05</td></tr>
<tr><td></td><td>Tyrvaya (n=46)</td><td>Vehicle (n=43)</td><td>Tyrvaya (n=255)</td><td>Vehicle (n=248)</td></tr>
<tr><td>Change from baseline in EDS at Day 28 (clinic setting)</td><td>-18.9 mm</td><td>-5.4 mm</td><td>-19.8 mm</td><td>-15.4 mm</td></tr>
<tr><td>p value vs. control</td><td colspan="2">0.01</td><td colspan="2">Not met</td></tr>
</table>
*Schirmer's Test Score (STS): Measure of tear production in the eye and performed by placing a filter paper in the lower eye lid. The distance tears travel down the paper is measured in millimeters from 0-35, with a higher score showing better outcomes.
**Corneal fluorescent staining: used to assess the tear film or damage to the eye, with a lower score showing better outcomes.
***Eye Dryness Score (EDS): Rated on a Visual Analog Scale from 0 (no discomfort) to 100 (maximum discomfort), with a lower score showing better outcomes.</td></tr>
<tr><td>SAFETY</td><td>Discussed in the Adverse Effects section below.</td></tr>
</table>

Contraindications [2]

- None

Warnings and Precautions [5]

- Pregnancy Considerations: Adverse events were not observed in animal reproduction studies after administration of oral varenicline. After nasal administration, varenicline is absorbed systemically with concentrations of ~7.5% of an oral 1 mg dose.
- Breastfeeding Considerations: It is unknown if varenicline is present in breast milk. According to the manufacturer, the decision to breastfeed should consider the risk of exposure to the infant, benefits of breastfeeding, and benefits of treatment for the mother.

Adverse Effects [5]

Most common, ≥5%	% of occurrence
Sneezing	82
Cough	16
Throat irritation	13
Nasal irritation	8

Drug Interactions [5]

- No known significant interactions.

Dosage and Administration [(2)]

- One spray in each nostril twice daily (approximately 12 hours apart).
- Priming required before initial use (7 pump actuations into the air away from the face) and if Tyrvaya has not been used for > 5 days (1 pump actuation into the air away from the face).
- If a dose is missed, resume regular dosing at next scheduled time.

Cost

Generic Name	Brand Name	Manufacturer	Dose	Cost**/ Month
Varenicline solution	Tyrvaya	Oyster Point Pharma, Inc.	0.03 mg varenicline per spray (0.05 mL)	$592

** Wholesale Acquisition Cost

Conclusion

Tyrvaya is the first nasal spray to treat DED approved by the FDA. The mechanism of this drug as an agonist at heteromeric sub-type(s) of the nicotinic acetylcholine receptor causes an increase in basal tear film. Tyrvaya's efficacy was displayed through the ONSET-1 and ONSET-2 trials, showing a significant increase in the Schirmer's score results. Adverse effects with Tyrvaya were common, but they were largely associated with administration and local effects.

Recommendation

This drug is being considered for inclusion in the state specific Preferred Drug List (PDL) as non-preferred.

References

1) IPD Analytics [Tyrvaya New Drug Review]. Published October 2021. Available at IPDanalytics.com. Accessed January 13, 2022.
2) Tyrvaya [package insert]. Princeton NJ: Oyster Point Pharma, Inc.; 2021.
3) Evaluation of the efficacy of OC-01 nasal spray on signs and symptoms of dry eye disease. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/study/NCT03636061. Published October 25, 2021. Accessed January 7, 2022.
4) Evaluation of the efficacy and safety of OC-01 nasal spray on signs and symptoms of dry eye disease. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/record/NCT04036292. Published November 22, 2021. Accessed January 7, 2022.
5) Varenicline (nasal). Lexicomp. https://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/7160133?cesid=0MwYzPBx9jz&searchUrl=%2Flco%2Faction%2Fsearch%3Fq%3Dtyrvaya%26t%3Dname%26va%3Dtyrvaya. Published November 10, 2021. Accessed January 7, 2022.

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