Acoltremon ophthalmic solution (TRYPTYR)
National Drug Monograph
August 2025

VA Pharmacy Benefits Management Services and VA National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information[1]

Description/Mechanism of Action

- Acoltremon is an agonist of transient receptor potential melastatin 8 (TRPM8) thermoreceptors. TRPM8 thermoreceptor stimulation has been shown to activate trigeminal nerve signaling leading to increased basal tear production.

Indication(s) Under Review in This Document

- Acoltremon is indicated for the treatment of the signs and symptoms of dry eye disease

Dosage Form(s) Under Review

- Ophthalmic solution: 0.003% acoltremon in a single-dose vial

Clinical Evidence Summary

Efficacy Considerations [1]

- The efficacy of acoltremon, supporting its FDA approval, was evaluated from industry-sponsored studies, including two phase 3 randomized, multicenter, double-masked, vehicle-controlled studies (COMET-2 [NCT05285644] and COMET-3 [NCT05360966])
- Patients were randomized to acoltremon or vehicle (placebo) in a 1:1 ratio and dosed twice a day for 90 days
- The mean age was 61 years (range, 30-93 years). Most patients were female (74.8%)
- Enrollment criteria included signs (i.e., corneal fluorescein staining score [2-15] and anesthetized Schirmer tear test [2-9 mm]) and symptoms (i.e., SANDE Score [≥ 50] and Ocular Discomfort Score [≥ 50]) of dry eye disease
- Tear film production was measured by unanesthetized Schirmer tear test assessed using a Schirmer strip (0 - 35 mm). The average baseline unanesthetized Schirmer scores for acoltremn and vehicle treated patients was 6.2 mm and 5.9 mm in the COMET-2 study, and 6.8 mm and 6.4 mm in the COMET-3 study, respectively (Table 1 and 2)
- The primary endpoint was the proportion of patients who achieved at least a 10mm increase in unanesthetized Schirmer score from baseline at day 14. A score of at least 10mm over time indicates a better outcome. Schirmer's test is a diagnostic procedure designed to measure the

amount of tear production in the eyes. It is straightforward and non-invasive. During the test, a small strip of specialized filter paper is gently placed inside your lower eyelid. The paper remains in place for approximately five minutes, during which it absorbs the tears your eyes produce. Afterward, the healthcare provider measures the length of the paper that has been moistened by your tears, which reflects your tear production levels.

- There are two variations of Schirmer's test: one performed without anesthetic eye drops and another with anesthetic drops. The version without anesthetic measures both reflex and basal tear production, while the version with anesthetic focuses exclusively on basal tear production. Reflex tears are produced in response to irritation or emotional stimuli, whereas basal tears provide continuous, protective moisture to maintain eye health. As noted above, patients were screened for eligibility with an anesthetized Schirmer test while baseline measurement utilized the unanesthetized variation. Patients included in COMET-2 and COMET-3 had average baseline Schirmer scores Test score between 5 mm and 10 mm reflecting mild to moderate dry eyes.[1,2]
- Of the patients treated at Day 14 (primary endpoint) with acoltremon, more patients achieved ≥ 10 mm increase in Schirmer score from baseline in the COMET-2 and COMET-3 studies compared to vehicle-treated patients (Table 3)

Table 1. Demographics, COMET-2

	Acoltremon N=230	Vehicle N=235
Age, mean (SD)	59.5 (13.04)	59.6 (13.43)
Sex: Female/Male	173/57	180/55
Ethnicity Hispanic or Latino Not Hispanic or Latino	 31 199	 34 201
Schirmer test pre-drop at baseline (Day 1) Mean (SD)	6.2 (5.49)	5.9 (5.41)

SD, standard deviation

Table 2. Demographic, COMET-3

	Acoltremon N=232	Vehicle N=234
Age, mean (SD)	63.1 (12.23)	62.1 (12.19)
Sex: Female/Male	177/55	166/68
Ethnicity Hispanic or Latino Not Hispanic or Latino	 16 216	 28 206
Schirmer test pre-drop at baseline (Day 1) Mean (SD)	6.8 (6.28)	6.4 (5.47)

SD, standard deviation

Table 3. Percent of patients achieving ≥ 10 mm improvement from baseline in Schirmer Score at day 14 in patients with Dry Eye disease[1]

Tear Production				
	COMET-2		COMET-3	
	Acoltremon N=230	Vehicle N=235	Acoltremon N=232	Vehicle N=234
≥10 mm increase in tear production at Day 14	42.6%	8.2%	53.2%	14.4%
Difference (95% CI)	34.4% (26.9, 42.0)		38.8% (30.8, 46.8)	
P-value versus vehicle	<0.01		<0.01	

N=total, CI=confidence interval

Safety Considerations[1]

Contraindications:

- None

Other warnings and precautions[1]

- Potential for eye injury and contamination
- Use with contact lenses – should not be administered while wearing contact lenses

Adverse Reactions (COMET-2, COMET-3)

The most common adverse reaction reported in clinical trials was instillation site pain.

Other Therapeutic Options

Table 4.

Drug	Formulary status	Clinical Guidance/ Indication
Acoltremon	NF	Dry eye
Artificial Tears (Multiple)	F	Dry eyes
Cyclosporine (Restasis)	F	Dry eye
Lifitegrast (Xiidra)	PA-F	Dry eye
Perfluorohexyloctane (Miebo)	NF	Dry eye
Varenicline (Tyrvaya)	NF	Dry eye

Projected Place in Therapy

- Dry eye is when your eyes do not produce enough tears. It may also be when your eyes do not make the right type of tears or when your tears dry out too quickly.

- Symptoms of dry eye may include burning, blurred vision, red irritated eyes, or a gritty feeling like something is in your eye.
- Dry eye may be caused by medical conditions, smoke, wind, long use of contact lenses, and certain medications. It is generally treated with artificial tears.
- COMET-2 and COMET-3 showed that more patients treated with acoltremon achieved ≥ 10 mm increase in Schirmer score from baseline (primary outcome) compared to vehicle-treated patients.
- Acoltremon is a mechanistically unique product that adds to the list of available agents used to treat dry eye.

References

1. TRYPTYR (Acoltremon ophthalmic solution) [prescribing information]. Alcon Laboratories, Inc. Fort Worth, TX 2025.
2. Brott NR, Zeppieri M, Ronquillo Y. Schirmer Test. StatPearls [Internet]. February 24, 2024. Accessed 6/17/2025. https://www.ncbi.nlm.nih.gov/sites/books/NBK559159/

Prepared August 2025. Contact person: Matthew A. Fuller, Pharm.D., BCPP, National PBM Clinical Pharmacy Program Manager, VA Pharmacy Benefits Management Services (12PBM)