Varenicline (TYRVAYA) Nasal Spray
National Drug Monograph
November 2022
VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

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

Description/Mechanism of Action
The lacrimal functional unit (LFU) is made up of the lacrimal gland, ocular surface (cornea, conjunctiva, meibomian glands), eyelids, and the interconnecting sensory and motor neurons. Parasympathetic activation of the LFU via the trigeminal nerve stimulates the production of the tear film. Varenicline is a selective cholinergic agonist. Intranasal administration activates the trigeminal parasympathetic pathway in the nasal cavity to stimulate basal tear film production.

Indication(s) Under Review in This Document
Treatment of the signs and symptoms of dry eye disease

Dosage Form(s) Under Review
- Nasal spray delivering 0.03mg of varenicline in each spray (0.05mL)
- Administered as one spray in each nostril twice daily approximately 12 hours apart
- Available in a carton containing two nasal spray glass bottles; each bottle supplies treatment for 15 days

Clinical Evidence Summary

Efficacy Considerations
Two pivotal 4-week trials (ONSET-1, ONSET-2) and one supportive 12-week trial (MYSTIC) compared varenicline nasal spray to vehicle in patients with dry eye disease.

Key inclusions: dry eye disease as measured by an anesthetized Schirmer's score of 10mm/5min or less and an Ocular Surface Disease Index (OSDI) score of at least 23, and corneal fluorescein staining (CFS) score of 2 or more in at least 1 corneal region, or a sum of 4 or more for all corneal regions, and wish to use or are using artificial tears.

Key exclusions: corneal epithelial defects; chronic or recurrent epistaxis, coagulation disorders; nasal or sinus surgery; vascularized polyp, severely deviated septum, chronic recurrent nosebleeds, or severe nasal obstruction; current treatment with nasal continuous positive airway pressure; any intraocular surgery, extraocular surgery in either eye within 3 months, or refractive surgery within 12 months; blepharoplasty or corneal transplant in either eye; use of contact lenses within 7 days before the study or anticipated use of contact lenses during the study; any form of punctal or intracanalicular occlusion.

Varenicline was studied using doses of 0.03mg and 0.06mg administered twice daily. Results for the marketed dose (0.03mg) are shown. Results for the higher dose did not offer an advantage over the marketed dose. Use of concomitant artificial tears was allowed during the study.

Outcomes in the ONSET trials include assessment of Schirmer's test score (STS) with anesthesia and Eye Dryness Score (Visual Analog Scale) (EDS-VAS). MYSTIC trial assessed STS with anesthesia.

The STS with local anesthesia assesses basal tear secretion. Wetting of the filter strip from 0-5mm indicates severe dry eye; 5-10mm moderate dry eye: 10-15mm mild dry eye; greater than 15mm is normal tear function. The EDS is a validated assessment tool where patients rate their dry eye symptoms using a visual analogue scale (0=no discomfort, 100=maximal discomfort). Values equal to or greater than 60 indicate moderate to severe disease. Based on another study, a change of -13mm is considered clinically meaningful. Eye dryness score was evaluated both in the Controlled Adverse Environment (CAE) and in the clinic environment.

Demographic and baseline values:

- ONSET 2: female 74%, mean age 61 years, baseline anesthetized Schirmer's score 5.1mm; baseline eye dryness score (EDS) 59.3, Ocular Surface Disease Index 51, corneal fluorescein staining (CFS) 6.2
- MYSTIC: female 81%, mean age 54 years, baseline anesthetized Schirmer's score 5.4mm

Onset of tear production was as early as 5 minutes after administration. There was significant improvement in the anesthetized Schirmer's Test score and significantly more patients had a change of 10mm or more with varenicline compared to vehicle at week 4 in the ONSET trials and at week 12 in the MYSTIC trial.

Symptoms of eye dryness as measured by EDS was significantly improved with varenicline compared to vehicle in the ONSET-1 trial both in the clinic and CAE environments. In ONSET-2, varenicline and vehicle had a clinically meaningful reduction in EDS in the clinic setting; however, the difference between varenicline and vehicle was considered statistically significant. In the CAE, improvement in EDS was not significantly different between varenicline and vehicle. This may be explained by the social distancing requirements during the coronavirus pandemic which restricted use of the CAE chamber because of the enclosed close-proximity chamber environment. This impacted collection of symptom data in approximately 30% of the study population.

The change from baseline in CFS (secondary endpoint) at week 4 with varenicline was not statistically significant compared to vehicle.

Table 1: Efficacy Results from Clinical Trials

Study	Treatments	Change in STS (mm)	>/=10mm change in STS (% pts)	EDS CAE (mm)	EDS clinic (mm)	Other
ONSET-1 (Phase 2b) 28 days	Varenicline (n=48) Vehicle (n=43) *Artificial tears allowed*	**11.8*** **3.2** *Results shown at 4 weeks*	52 14 *Results shown at 4 weeks*	-16* -4.4 *Results shown at 3 weeks*	-16.0*/-18.9* -6.3/-5.4 *Results shown at 3 weeks/4 weeks*	Long-term f/u at 6 and 12 months for this study (data currently not available)
ONSET-2 (Phase 3) 28 days	Varenicline (n=260) Vehicle (n=252) *Artificial tears allowed*	11.3* 6.3 *Results shown at 4 weeks*	**47*** **28** *Results shown at 4 weeks*	-10.3mm -7.4mm *Results shown at 4 weeks*	-16.5/-19.8* -12.7/-15.4 *Results shown at 2 weeks/4 weeks*	
MYSTIC (Phase 2) Supportive study	Varenicline (n=41) Vehicle (n=41) *Artificial tears allowed*	**11.0*** **6.0** *Results shown at 12 weeks*	49 24 *Results shown at 12 weeks*	NA	NA	Change in STS (mm) Varenicline; Vehicle •Week 1: 11.6; 6.5 •Week 8: 10.7; 6.1

Abbreviations: CAE=controlled adverse environment; EDS=Eye dryness score (0-100 visual analog scale; 0=no discomfort, 100=maximal discomfort); NA=not applicable; STS= Schirmer's Test Score (anesthetized)
*Statistically significant vs vehicle
BOLDED results indicate primary outcome

Safety Considerations

Safety Results from Clinical Trials:

Sneezing was the most commonly reported adverse event occurring in 82% of patients in the pooled ONSET-1 and ONSET-2 data sets. Among those who reported sneezing, 98% reported it as mild. In ONSET-2, 65% of sneezing resolved within 1-2 minutes. No patients discontinued varenicline due to sneezing. Table 2 shows adverse events reported in the ONSET-2 trial.

Table 2: Safety results from ONSET-2

	Varenicline (n=**260**)	**Vehicle** (n=**251**)
Sneezing (%)	95	29
Cough (%)	18.8	2.0
Throat irritation (%)	13.5	2.0
Instillation site irritation (%)	8.1	1.2
Nasopharyngitis (%)	3.5	5.6

- **Boxed warnings:** None
- **Contraindications:** None
- **Other warnings/precautions**: None
- **Adverse reactions**
  - **Common:** sneezing (82%); cough (16%); throat irritation (13%); instillation-site (nose) irritation (8%)
  - **Serious Adverse events:** None (ONSET-2)
  - **Deaths:** ONSET-2 Three deaths unrelated to study drug (pneumonia, cerebrovascular accident, coronavirus infection) which occurred during post-treatment follow-up period.
  - **Discontinuation due to adverse events:** Across all studies 7/349 (2%) varenicline vs 7/335 (2.1%) vehicle

Other Considerations

- Long term data needed. Currently 84-day data are available from the MYSTIC trial in a small number of patients.
- Unknown if tolerance develops over time as seen with external electromechanical nerve stimulator devices (iTEAR100)
- There is a potential for administration errors. Administration of varenicline differs from other nasal sprays.
  - Insert the nasal applicator into the left or right nostril. Tilt the nasal applicator and point the tip of the nasal applicator towards the top of the ear on the same side as your nostril.
  - Do not press the tip of the nasal applicator against the wall of the inside of your nose. Leave a space between the tip of the nasal applicator and the wall of the inside of your nose.
  - Place your tongue to the roof of your mouth and breathe gently while pressing and releasing the nasal applicator 1-time to release a spray into your nostril.
- In Clinicaltrials.gov no trials were listed comparing varenicline to topical agents such as cyclosporine A or lifitegrast
- Other areas of research: neurotrophic keratopathy, dry eye associated with contact lens intolerance, and ocular surface preparation for refractive surgeries.

Other Therapeutic Options

Alternative drugs, excluding artificial tears and topical steroids, for treatment of dry eye disease are listed in table 3.

Table 3 Treatment Alternatives (excludes artificial tears and topical steroids)

Drug	Formulary Status	Clinical Guidance
Varenicline nasal spray	TBD	• Cholinergic agonist • Treatment of signs and symptoms of dry eye disease • Meaningful increase in production of basal tear film as early as 4 weeks • Most common AEs: sneezing (82%) cough (16%); throat irritation (13%); instillation-site (nose) irritation (8%)
Cyclosporine 0.05% emulsion	PA-F	• Immunomodulator • To Increase tear production in those with keratoconjunctivitis sicca (dry eye) • Can take 3-6 months to notice increase in tear production or symptom improvement • Most common AE: ocular burning 17%
Cyclosporine 0.09% solution	NF	• Immunomodulator • To Increase tear production in those with keratoconjunctivitis sicca (dry eye) • Most common AEs: instillation site pain 22%; hyperemia 6%
Lifitegrast solution	PA-F	• Immunomodulator • Treatment of signs and symptoms of dry eye disease • Symptom relief can begin as early as 2 weeks • Most common AEs: instillation site irritation 15.2%; instillation site reaction 12.3%; instillation site pain 9.8%; dysgeusia 14.5%

AE=adverse events; CFS=corneal fluorescein staining; CsA= cyclosporine A; EDS=eye dryness score; ICSS=inferior corneal staining score; STS=Schirmer's Test score; TD=treatment difference

**Trial results not intended for direct comparison as study design, patient population, treatment endpoints, etc. differed among trials

Projected Place in Therapy

Patients with dry eye disease who have not responded or tolerated treatment with topical cyclosporine and lifitegrast.

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