PHARMACY COVERAGE GUIDELINE

CEQUA® (cyclosporine) ophthalmic solution
MIEBO™ (perfluorohexyloctane) ophthalmic solution
RESTASIS® (cyclosporine) ophthalmic emulsion
TYRVAYA™ (varenicline) nasal solution
VEVYE® (cyclosporine) ophthalmic solution
XIIDRA™ (lifitegrast) ophthalmic solution
Generic Equivalent (if available)

This Pharmacy Coverage Guideline (PCG):
- Provides information about the reasons, basis, and information sources we use for coverage decisions
- Is not an opinion that a drug (collectively "Service") is clinically appropriate or inappropriate for a patient
- Is not a substitute for a provider's judgment (Provider and patient are responsible for all decisions about appropriateness of care)
- Is subject to all provisions e.g. (benefit coverage, limits, and exclusions) in the member's benefit plan; and
- Is subject to change as new information becomes available.

Scope
- This PCG applies to Commercial and Marketplace plans
- This PCG does not apply to the Federal Employee Program, Medicare Advantage, Medicaid or members of out-of-state Blue Cross and/or Blue Shield Plans

Instructions & Guidance
- To determine whether a member is eligible for the Service, read the entire PCG.
- This PCG is used for FDA approved indications including, but not limited to, a diagnosis and/or treatment with dosing, frequency, and duration.
- Use of a drug outside the FDA approved guidelines, refer to the appropriate Off-Label Use policy.
- The "Criteria" section outlines the factors and information we use to decide if the Service is medically necessary as defined in the Member's benefit plan.
- The "Description" section describes the Service.
- The "Definition" section defines certain words, terms or items within the policy and may include tables and charts.
- The "Resources" section lists the information and materials we considered in developing this PCG
- **We do not accept patient use of samples as evidence of an initial course of treatment, justification for continuation of therapy, or evidence of adequate trial and failure.**
- Information about medications that require prior authorization is available at www.azblue.com/pharmacy. You must fully complete the request form and provide chart notes, lab workup and any other supporting documentation. The prescribing provider must sign the form. Fax the form to BCBSAZ Pharmacy Management at (602) 864-3126 or email it to Pharmacyprecert@azblue.com.

Criteria:

TYRVAYA (varenicline)

- **Criteria for initial therapy:** Tyrvaya (varenicline) nasal spray and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

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1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Ophthalmologist or Optometrist

2. Individual is 18 years of age or older

3. Individual has a confirmed diagnosis of moderate to severe dry eye disease (DED) determined by **ONE** of the following:
    a. Schirmer test (aqueous tear production and clearance)
    b. Tear break-up time
    c. Ocular surface dye staining
    d. Tear film osmolarity
    e. Fluorescein clearance test / tear function test

4. Individual has documented failure of at least 3 months, contraindication per FDA label, intolerance, or is not a candidate for **ALL** of the following:
    a. Artificial tears
    b. Generic cyclosporine 0.05%

5. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

6. Artificial tears product will be continued

7. Will not be used concurrently with an ophthalmic cyclosporine product (Restasis and generic, Cequa, Vevye), Miebo, or Xiidra

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Tyrvaya (varenicline) and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** the following criteria are met **(samples are not considered for continuation of therapy)**:

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation with an Ophthalmologist or Optometrist

2. Individual's condition has responded while on therapy with response defined as **THREE** of the following:
    a. No evidence of disease progression
    b. Achieved and maintains improvement in tear production over baseline
    c. Achieved and maintains improvement in DED signs and symptoms over baseline
    d. Achieved and maintains at least a ≥ 10 mm improvement in Schirmer's Test Score (STS)

3. Individual has been adherent with the medication **and** the artificial tears product

4. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Will not be used concurrently with an ophthalmic cyclosporine product (Restasis and generic, Cequa, Vevye), Miebo, or Xiidra

Renewal duration: 12 months

- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

1. **Off-Label Use of Non-Cancer Medications**

2. **Off-Label Use of Cancer Medications**

CEQUA (cyclosporine)
MIEBO (perfluorohexyloctane)
RESTASIS (cyclosporine)
VEVYE (cyclosporine)
XIIDRA (lifitegrast)

- **Criteria for initial therapy:** Cequa (cyclosporine), Miebo (perfluorohexyloctane), Restasis (cyclosporine), Vevye (cyclosporine), Xiidra (lifitegrast) and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met:

1. Prescriber is a physician specializing in the patient's diagnosis or is in consultation with an Ophthalmologist or Optometrist

2. Individual age is **ONE** of the following:
   a. 16 years of age or older for Restasis
   b. 17 years of age or older for Xiidra
   c. 18 years of age or older for Cequa, Vevye, Miebo

3. Individual has a confirmed diagnosis of moderate to severe dry eye disease (DED) determined by **ONE** of the following diagnostic tests:
   a. Schirmer test (aqueous tear production and clearance)

b. Tear break-up time
c. Ocular surface dye staining
d. Tear film osmolarity
e. Fluorescein clearance test / tear function test

4. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

5. Individual has documented failure of at least 3 months, contraindication per FDA label, intolerance, or is not a candidate for **BOTH** of the following:
   a. Artificial tears
   b. Generic cyclosporine 0.05%

6. Artificial tears product will be continued

Initial approval duration: 6 months

- **Criteria for continuation of coverage (renewal request):** Cequa (cyclosporine), Miebo (perfluorohexyloctane), Restasis (cyclosporine), Vevye (cyclosporine), Xiidra (lifitegrast) and/or generic equivalent (if available) are considered ***medically necessary*** and will be approved when **ALL** of the following criteria are met **(samples are not considered for continuation of therapy)**

1. Individual continues to be seen by a physician specializing in the patient's diagnosis or is in consultation an Ophthalmologist or Optometrist

2. Individual's condition has responded while on therapy with response defined as **THREE** of the following:
   a. No evidence of disease progression
   b. Achieved and maintains improvement in tear production over baseline
   c. Achieved and maintains improvement in DED signs and symptoms over baseline
   d. Achieved and maintains at least a ≥ 10 mm improvement in Schirmer's Test Score (STS)

3. Individual has been adherent with the medication **and** the artificial tears product

4. **If available**: Individual has failure after adequate trial, contraindication per FDA label, intolerance, or is not a candidate for a **generic equivalent** [Note: Failure, contraindication or intolerance to the generic should be reported to the FDA] (see Definitions section)

Renewal duration: 12 months

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- Criteria for a request for non-FDA use or indication, treatment with dosing, frequency, or duration outside the FDA-approved dosing, frequency, and duration, refer to one of the following Pharmacy Coverage Guideline:

  1. **Off-Label Use of Non-Cancer Medications**

  2. **Off-Label Use of Cancer Medications**

Description:

Cequa (cyclosporine solution) 0.09% is a calcineurin inhibitor immunosuppressant indicated to increase tear production in patients with keratoconjunctivitis sicca (dry eye). Other names for dry eye include dry eye syndrome, keratoconjunctivitis sicca (KCS), and dysfunctional tear syndrome.

Cyclosporine (as a 0.05% emulsion found in brand Restasis and generics and as a 0.1% solution found in Vevye) is a calcineurin inhibitor immunosuppressant indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.

Miebo (perfluorohexyloctane ophthalmic solution) is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

Tyrvaya (varenicline solution) nasal spray is indicated for the treatment of the signs and symptoms of DED.

Xiidra (lifitegrast ophthalmic solution) 5% is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

Cyclosporine is an immunosuppressive agent when administered systemically. In patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca, cyclosporine emulsion is thought to act as a partial immunomodulator. The exact mechanism of action is not known.

Lifitegrast binds to the integrin lymphocyte function-associated antigen-1 (LFA-1), a cell surface protein found on leukocytes. Lifitegrast blocks the interaction of LFA-1 with intercellular adhesion molecule-1 (ICAM-1). ICAM-1 may be overexpressed in corneal and conjunctival tissues in DED. The interaction of LFA-1 and ICAM-1 can contribute to the formation of an immunological synapse resulting in T-cell activation and migration to target tissues. *In vitro* studies demonstrated that lifitegrast may inhibit T-cell adhesion to ICAM-1 in a human T-cell line and may inhibit secretion of inflammatory cytokines. The exact mechanism of action of lifitegrast in DED is not known.

The efficacy of varenicline in DED is believed to be the result of varenicline's activity at heteromeric sub-type(s) of the nicotinic acetylcholine (nACh) receptor where its binding produces agonist activity and activates the trigeminal parasympathetic pathway resulting in increased production of basal tear film. Varenicline binds with high affinity

and selectivity and is a partial nACh receptor agonist of α4β2, α4α6β2, α3β4, and α3α5β4 receptors and a full α7 receptor agonist. The exact mechanism of action is unknown at this time.

Perfluorohexyloctane, a semifluorinated alkane, contains 6 perfluorinated carbon atoms and 8 hydrogenated carbon atoms. Perfluorohexyloctane forms a monolayer at the air-liquid interface of the tear film which can be expected to reduce evaporation. The exact mechanism of action for MIEBO in DED is not known.

DED is a multifactorial disease of the tears and ocular surface that results in ocular discomfort and visual impairment. DED can be due to ocular surface inflammation, altered tear-film composition, reduced tear production, poor lid function, environmental conditions, or diseases such as Sjögren's syndrome, meibomian gland dysfunction, or allergies. Medications such as anticholinergic drugs, antihistamines, nasal decongestants, estrogens, and many antidepressants can also cause dry eyes.

Patients may present with symptoms of chronic eye irritation associated with mild to moderate discomfort. Most patients present with symptoms of chronic eye irritation, such as eye dryness, red eyes, and burning sensation. Other common eye complaints may include general irritation, gritty sensation, foreign body sensation, excessive tearing, light sensitivity, and blurred vision.

The diagnosis of DED requires examination of the surface of the eye with a biomicroscope (also called a slit lamp). Schirmer's test quantifies tear production of each eye to determine whether the tear glands produce enough tears to keep eyes adequately moist. Results are measured in millimeters of tears collected over a five-minute time period. Wetting of less than 5 mm is indicative of deficient tear production. Ocular surface staining with fluorescein can facilitate evaluation of the tear film and demonstrate areas of damage on the ocular surface. It disperses in tear film and the longer the duration in which the dye remains evenly dispersed in the tear film, the better the quality of the tear film. The time that it takes for this tear film to “break up” or (TBUT) is an important measure of tear film integrity, a TBUT under 10 seconds is considered abnormal.

Treatment of dry eye disease is aimed at increasing or supplementing tear production, slowing tear evaporation, reducing tear resorption, or reducing ocular surface inflammation. The patient should discontinue unnecessary systemic or ocular medications that can contribute to dryness.

Artificial tears are considered first-line treatment for DED. There are several product formulations available. Preservative free forms are available for DED patients who have reactions to preservatives. Topical immune suppressants are second line and include topical cyclosporine and topical lifitegrast. Use of nasal varenicline is a newer form of delivery of medication and has a different mechanism of action that may be used if topical agents prove unsuccessful.

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Definitions:

U.S. Food and Drug Administration (FDA) MedWatch Forms for FDA Safety Reporting
MedWatch Forms for FDA Safety Reporting | FDA

Resources:

Restasis (cyclosporine) 0.05% ophthalmic emulsion product information, revised by Allergan, Inc. 09-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 27, 2024.

Cequa (cyclosporine) 0.09% ophthalmic solution/drops product information, revised by Sun Pharmaceutical Industries, Inc. 07-2022. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 27, 2024.

Vevye (cyclosporine) 0.1% ophthalmic solution/drops product information, revised by Harrow Eye, LLC. 11-2023. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 27, 2024.

Miebo (perfluorohexyloctane) ophthalmic 100% solution product information, revised by Bausch & Lomb Incorporated. 01-2024. Available at DailyMed http://dailymed.nlm.nih.gov. Accessed November 27, 2024.

Tyrvaya (varenicline) 0.03 mg per spray nasal spray product information, revised by Oyster Point Pharma 02-2024, at DailyMed http://dailymed.nlm.nih.gov. Accessed November 27, 2024.

Xiidra (lifitegrast) 5% ophthalmic solution/drops product information, revised by Bausch & Lomb Incorporated 12-2023, at DailyMed http://dailymed.nlm.nih.gov. Accessed November 27, 2024.

Shtein RM. Dry eye disease. In: UpToDate, Jacobs DS, Li H (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through December 2024. Topic last updated August 07, 2024. Accessed January 08, 2025.

Baer AN, Akpek EK. Treatment of moderate to severe dry eye in Sjogren's syndrome. In: UpToDate, Fox R, Seo P (Eds), UpToDate, Waltham MA.: UpToDate Inc. Available at http://uptodate.com. Literature current through December 2024. Topic last updated March 29, 2024. Accessed January 08, 2025.

Alpek EK, Amescua G, Faird M, et al.: Dry Eye Syndrome Preferred Practice Pattern. Ophthalmology. 2019 Jan;126 (1):286-334. Accessed January 27, 2024. Re-evaluated January 08, 2025.