Ophthalmic Immunomodulatory Agents
Cyclosporine 0.05% Ophthalmic Emulsion (Restasis)

Executive Summary

- The ophthalmic immunomodulatory agents have not previously been reviewed for Uniform Formulary (UF) placement. Restasis is the only drug in this UF drug subclass.
- Restasis in the only FDA-approved agent indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca (KCS).
- Cyclosporine ophthalmic emulsion provides a disease-modulating effect on inflammation that is found with moderate to severe dry eye disease. The ability to alter the inflammatory process is important in managing KCS.
- Restasis does not increase tear production in those taking topical anti-inflammatory drugs or using punctal plugs.
- The safety profile of ophthalmic cyclosporine has no serious concerns and had low dropout rates in clinical studies. Evaluation of blood levels to assess systemic absorption from the ocular cyclosporine emulsion has demonstrated that no active drug crosses into the systemic circulation; there are few concerns for systemic toxicity.
- Dosing of this ophthalmic emulsion is twice daily and can be used with artificial tears.

Background

The treatment of KCS varies by degree of the disease and the causative process. Initially, various non-pharmacologic methods are employed such as eyelid hygiene and avoidance of aggravating factors. Artificial tears are first-line therapy for patients with mild to moderate dry eye disease. However, the use of tear supplements is symptomatic and does not alter the course of the disease. Ophthalmic cyclosporine emulsion is the only pharmacologic treatment that is FDA approved specifically for dry eye disease. It is a disease modifying therapy and not palliative. The American Academy of Ophthalmology, in 2013, stated that cyclosporine is appropriate for use in patients who have moderate to severe dry eye disease severity. Additionally, dry eye is a life-long condition whose symptoms and signs wax and wane. Cost considerations and lack of long-term efficacy data are important factors in the decision to prescribe cyclosporine.

Table 1: Drugs in the Ophthalmic Immunomodulatory Agent Subclass

Cyclosporine	Restasis (Allergan)	0.05% ophthalmic emulsion	Dec 2002	2024

Indication

Restasis is a topical immunomodulator indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

Efficacy

Cyclosporine ophthalmic emulsion is effective in the treatment of moderate to severe dry eye disease, improving both objective and subjective measures. Objective measures included corneal fluorescein staining and Schirmer's test. Corneal fluorescein staining is used to evaluate the tear film and areas of damage on the ocular surface and Schirmer's test, with and without anesthesia, is used to determine whether the eye produces enough tears to keep it moist. For both of these objective endpoints, improvement was significantly greater in the cyclosporine group compared to the group using only the vehicle (placebo group).

Corneal fluorescein staining	▪ Significant improvement from baseline in corneal staining in all treatment groups at all follow-up visits ($p<0.001$) ▪ Improvement was significantly greater in both CsA groups versus vehicle ($p<0.044$) at month 4 and in the CsA 0.05% group at month 6 ($p=0.008$)
Schirmer test with and without anesthesia	▪ At month 6, statistically significant improvements in Schirmer values (with anesthesia) from baseline with both CsA groups, and changes in each group were significantly greater versus vehicle ($p<0.007$) ▪ Also, statistically significant improvements without anesthesia within all study groups at all visits
CsA = cyclosporine A	

Subjective endpoints included an Ocular Surface Disease Index questionnaire, a facial expression rating scale, measurements of dry eye symptoms, an investigator's evaluation of global response to treatment, and a need for artificial tears. All subjective endpoints demonstrated statistically significant improvements in the cyclosporine arm versus the vehicle (placebo) arm of the study.

Ocular Surface Disease Index (OSDI)	▪ Statistically significant improvements from baseline (p<0.001)
Facial expression subjective rating scale	▪ Statistically significant improvements from baseline (p<0.001)
Symptoms of dry eye	▪ For blurred vision, CsA 0.05% group had statistically significant greater improvement than the vehicle group at all follow-up visits (p<0.014) ▪ Statistically significant changes from baseline were observed within all treatment groups at all time points in dryness (p<0.001), sandy/gritty feeling (p<0.001), and itching (p≤0.038)
Investigator's evaluation of global response to treatment	▪ Significantly greater improvements in the physician's evaluation of global response to treatment (p<0.05)
Need for artificial tears	▪ Patients in the CsA 0.05% group reported a statistically significant decrease in the need for supplemental artificial tears products at months 3, 4, and 6 (p ≤0.002)
CsA = Cyclosporine A	

Safety

The most common treatment-related adverse events were ocular burning and stinging. The treatment-related adverse events were as follows: 25.3% for CsA 0.05%, 29.1% for CsA 0.1%, and 19.5% for vehicle. Adverse event rates for burning for CsA 0.05%, CsA 0.1%, and vehicle were 14.7%, 16.1%, and 6.5% respectively. Adverse event rates for stinging CsA 0.05%, CsA 0.1%, and vehicle were 3.4 %, 4.5%, and 1.4% respectively. There were no significant topical or systemic adverse safety findings.

Overall, the efficacy results of the trial comparing Restasis to vehicle showed that this ophthalmic emulsion was well tolerated and effective in the treatment of moderate to severe dry eye disease. This was evident through improvements in both objective and subjective measures. Improvements seen in the subjective measures (of blurred vision and use of artificial tears) demonstrated that the changes seen in the objective endpoints resulted in benefits that decreased patients' needs for palliative treatments. For safety, there was a very low rate of treatment-related adverse events; those that were seen were mild to moderate in nature and transient.

References

1. Restasis® (cyclosporine ophthalmic emulsion 0.05%). Product labeling. Allergan. December 2013.
2. Sall K, Stevenson OD, Mundorf TK, Reis BL. Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. CsA Phase 3 Study Group. *Ophthalmology*. 2000 Apr;107(4):631-9.

Abbreviations

The following abbreviations are used in this review:

CsA – Cyclosporin**e** A
KCS – keratoconjunctivitis sicca
UF – Uniform Formulary