CLINICAL UPDATE

Brand Name	Eysuvis™
Generic Name	loteprednol etabonate
Drug Manufacturer	Kala Pharmaceuticals, Inc

Clinical Update

TYPE OF CLINICAL UPDATE

New Brand and Strength

FDA APPROVAL DATE

October 26, 2020

LAUNCH DATE

November 20, 2020

REVIEW DESIGNATION

Standard

TYPE OF REVIEW

New Drug Application (NDA): 210933

DISPENSING RESTRICTIONS

Open Distribution

Overview

INDICATION(S) FOR USE

Eysuvis™ is a corticosteroid indicated for the short-term (up to two weeks) treatment of the signs and symptoms of dry eye disease.

MECHANISMS OF ACTION

Corticosteroids inhibit the inflammatory response to a variety of inciting agents and delay or slow healing. They inhibit the edema, fibrin deposition, capillary dilation, leukocyte migration, capillary proliferation, fibroblast proliferation, deposition of collagen, and scar formation associated with inflammation. They are also thought to inhibit prostaglandin production.

DOSAGE FORM(S) AND STRENGTH(S)

Ophthalmic suspension containing 2.5 mg/mL of loteprednol etabonate.

DOSE & ADMINISTRATION

- Shake for two to three seconds before using.
- Instill one to two drops into each eye four times daily.

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EFFICACY

The safety and efficacy of Eysuvis™ was evaluated in one Phase 2 and three Phase 3 (STRIDE 1, STRIDE 2, and STRIDE 3) randomized, double-blind, placebo-controlled trials. In the Phase 3 studies, patients received Eysuvis™ or vehicle (1:1) four times daily for 2 weeks. The primary endpoints for STRIDE 1 and STRIDE 2 included the mean change from baseline in ocular discomfort severity (ODS) score and the mean change from baseline in conjunctival hyperemia at Day 15 in the overall intent-to-treat (ITT) population. In STRIDE 3, the primary endpoint was the mean change from baseline in ODS score at Day 15 in the ITT population and in a predefined subgroup of ITT patients with more severe ocular discomfort (ODS >68) at baseline.

The study design and population for the three Phase 3 trials are provided in Table 1.

Table 1. STRIDE 1, STRIDE 2, and STRIDE 3 Study Design

Study Population	• Documented clinical diagnosis of DED in both eyes • 18 years of age and older **Key Exclusion Criteria:** • History of glaucoma, IOP >21 mmHg at the screening or randomization visits or being treated for glaucoma in either eye • Diagnosis of ongoing ocular infection or severe/serious ocular condition that, in the judgment of the investigator, could confound study assessments or limit compliance • Have been exposed to an investigational drug within 30 days prior to screening
Interventions	• Eysuvis 0.25% or vehicle (1:1 ratio), one to two drops instilled in each eye four times daily (QID) for 2 weeks • The use of artificial tears was not allowed during the trials
Endpoints	**STRIDE 1 and STRIDE 2:** • Comparison of the mean bulbar conjunctival hyperemia between Eysuvis and vehicle using a 0–4 grading scale (higher number indicating more severity) at Day 15 • Comparison of mean ocular discomfort severity (ODS)* between Eysuvis and vehicle at Day 15 **STRIDE 3:** Comparison of mean ODS between Eysuvis and vehicle at Day 15

*ODS was rated by patients daily over the course of the trial using a visual analog scale (0=very mild, 100=very severe).

The results from the Phase 3 trials are provided in Tables 2 and 3.

STRIDE 1 demonstrated statistically significant changes in conjunctival hyperemia and ODS compared to vehicle from baseline to Day 15. However, STRIDE 2 only demonstrated a statistically significant change in hyperemia compared to vehicle but not in ODS. In STRIDE 3, statistically significant improvements in ODS were demonstrated in the ITT population and in the predefined subgroup, with more severe ocular discomfort at baseline. Patients receiving Eysuvis™ in STRIDE 3 also showed statistically significant improvement in conjunctival hyperemia, which was a key secondary endpoint in this trial.

The clinical significance of a ~4-point difference between Eysuvis™ and vehicle in the ODS score outside of a clinical trial in a real-world setting is unknown.

Table 2. Mean Change (SD) from Baseline in Ocular Discomfort Severity Score (ODS)			
	Vehicle	Eysuvis	Difference (95% CI)
	STRIDE 1		
	N=456	N=459	
Baseline	69.26 (15.38)	68.93 (15.89)	
Day 8	–4.81 (14.85)	–8.12 (16.88)	–3.38 (–5.40, –1.36)
Day 15	–9.16 (17.92)	–14.53 (20.64)	–5.43 (–7.92, –2.95)
	STRIDE 2		
	N=453	N=452	
Baseline	68.70 (15.80)	68.79 (15.46)	
Day 8	–4.86 (14.91)	–6.92 (15.34)	–2.05 (–4.01, –0.09)
Day 15	–9.24 (17.00)	–11.14 (19.90)	–1.87 (–4.30, 0.55)
	STRIDE 3		
	N=454	N=447	
Baseline	74.13 (12.73)	74.28 (13.02)	
Day 8	–5.83 (15.18)	–8.05 (15.01)	–2.18 (–4.13, –0.23)
Day 15	–8.91 (17.58)	–13.58 (19.38)	–4.67 (–7.08, –2.26)

Table 3. Mean Change (SD) from Baseline in Conjunctival Hyperemia			
	Vehicle	Eysuvis	Difference (95% CI)
	STRIDE 1		
	N=456	N=459	
Baseline	1.97 (0.62)	1.97 (0.60)	
Day 15	–0.16 (0.61)	–0.40 (0.65)	–0.25 (–0.33, –0.18)
	STRIDE 2		
	N=453	N=452	
Baseline	2.04 (0.57)	2.00 (0.62)	
Day 15	–0.24 (0.62)	–0.38 (0.61)	–0.16 (–0.23, –0.09)
	STRIDE 3		
	N=454	N=447	
Baseline	2.11 (0.61)	2.08 (0.64)	
Day 15	–0.18 (0.55)	–0.35 (0.58)	–0.18 (–0.24, –0.12)