NEW DRUG APPROVAL

Brand Name	Verkazia®
Generic Name	cyclosporine ophthalmic emulsion
Drug Manufacturer	Santen Inc.

New Drug Approval

FDA Approval Date: June 23, 2021

Review designation: Standard; Orphan

Type of review: Type 5 - New Formulation or New Manufacturer; New Drug Application (NDA): 214965

Dispensing restriction: N/A

Place in Therapy

DISEASE DESCRIPTION & EPIDEMIOLOGY

Vernal keratoconjunctivitis (VKC) is a type of ocular allergy. There are five main types of ocular allergy: seasonal allergic conjunctivitis (SAC), perennial allergic conjunctivitis (PAC), vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis (AKC), and giant papillary conjunctivitis (GPC). VKC and AKC are chronic, bilateral, and severe forms of allergic inflammation affecting the ocular surface. These two relatively uncommon types of allergic eye disease can cause severe damage to the ocular surface, leading to corneal scarring and vision loss if not treated properly (this occurs more commonly with AKC than VKC).

VKC is associated with other atopic manifestations in approximately one-half of patients; however, atopy is not necessarily related to the underlying pathogenesis of this condition. The most common concomitant atopic diseases are asthma and allergic rhinitis. Aeroallergen sensitization by skin prick testing or allergen-specific immunoassay was reported in over 50 percent of patients in one study. A family history of atopy was also reported in approximately one-half of patients in two studies. In another study, atopy was more common in patients with the palpebral or tarsal form of the disease compared with the limbal form. VKC was associated with a family history of other inflammatory diseases, such as psoriasis and thyroiditis, in one series.

VKC most commonly occurs in boys living in warm, dry, subtropical climates, such as the Mediterranean, the Middle East, Central and West Africa, South America, and Asian countries, such as Japan, Thailand, and India. The limbal form of VKC is seen most often in dark-skinned individuals from Africa and India. VKC is generally rare in cooler climates, such as Northern Europe and the temperate areas of North America. In the past, prevalence in these regions has been approximately 0.03 percent of the population. As an example, prevalence for Western Europe was 3.2 in 10,000, whereas a higher prevalence ranging from 2.4 to 27.8 in 10,000 was seen in Italy, a country with a Mediterranean climate. However, the prevalence in cooler regions has increased, probably due to immigration of individuals from susceptible populations.

Males are more commonly affected than females. In one series, the male-to-female ratio was 3.2:1 in patients <20 years of age but was nearly equal in older patients. Age at onset is generally before 10 years, with the earliest reported onset at five months of age, although VKC can infrequently occur in adults. Patients usually "outgrow" the disease with the onset of puberty.

Efficacy

The safety and efficacy of Verkazia® for the treatment of VKC was evaluated in two randomized, multi-center, double-masked, vehicle-controlled, clinical trials (VEKTIS Study NCT01751126 and NOVATIVE Study NCT00328653).

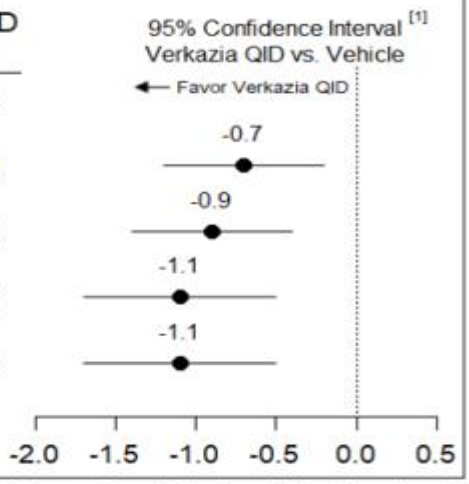
In the VEKTIS study, patients with severe VKC were randomized to four times daily of Verkazia® 1 mg/mL or two times daily (BID) of Verkazia® 1 mg/mL and vehicle group for the first 4 months (Period 1). Similarly, in the NOVATIVE study, patients with moderate to severe VKC were randomized to QID of Verkazia® 1 mg/mL or QID of cyclosporine ophthalmic emulsion 0.5 mg/mL) and vehicle group for the first 1 month (Period 1). In both studies, patients randomized to the vehicle group were switched to Verkazia® (QID or BID) from Month 4 to Month 12 in VEKTIS Study and to cyclosporine ophthalmic emulsion 0.5 mg/mL QID or 1 mg/mL from Month 1 to Month 4 in NOVATIVE Study (Period 2).

A total of 168 and 118 patients were enrolled in the VEKTIS and NOVATIVE studies for the efficacy analyses, respectively. Patients' age ranged from 4 through 17 years (mean age 9 years) in VEKTIS and 4 through 21 years (mean age 9 years) in NOVATIVE, with most patients being between 4 and 11 years of age (76% in VEKTIS and 80% in NOVATIVE) and male (79% in VEKTIS and 81% in NOVATIVE). Most of the patients had both limbal and tarsal forms of VKC (65% in VEKTIS and 74% in NOVATIVE). In both studies, patients had experienced VKC for a mean of 3 years prior to enrolment and all patients had a history of at least one recurrence of VKC in the year prior to study entry.

In the VEKTIS study, key efficacy evaluation was based on the change in corneal fluorescein staining (CFS) score and in itching score over 4 months. The results at each month are presented in Table 1 for the CFS score and in Table 2 for the Itching score.

Table 1: Efficacy Results of the Mean Change in Keratitis Score from Baseline at Each Visit(Full Analysis Set)

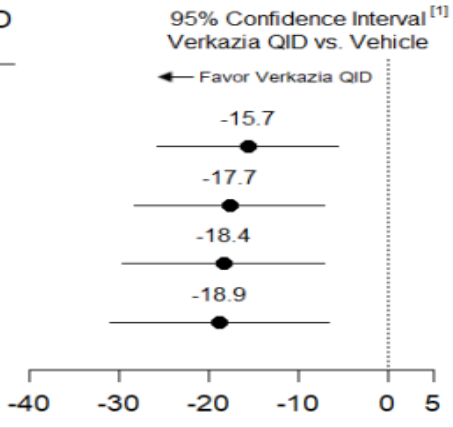
Visit	Vehicle (N = 58)	Verkazia QID (N = 56)	Verkazia BID (N = 54)
Baseline	4.1 (0.3)	4.3 (0.4)	4.1 (0.3)
Month 1	-0.8 (1.3)	-1.4 (1.4)	-1.3 (1.3)
Month 2	-0.9 (1.2)	-1.8 (1.5)	-1.8 (1.5)
Month 3	-1.2 (1.5)	-2.3 (1.6)	-2.0 (1.6)
Month 4	-1.2 (1.5)	-2.3 (1.7)	-1.9 (1.6)



[1] Treatment differences (numbers in the middle of the horizontal lines) and 95% confidence intervals (horizonatl lines) are based on ANCOVA model including baseline CFS score and the proportion of time potentially spent in taking study medication during the VKC season as covariate. For subjects that received rescue therapy during the study, all post-rescue data were imputed by the last available data observed prior to rescue initiation.
Note 1: CFS score was measured at each month using a 5-point scale (0=no stain, and 5 = more stain).
Note 2: The Full Analysis Set included all randomized subjects that received at least one drop of study medication.

Table 2: Efficacy Results of the Mean Change in Itching Score from Baseline at Each Visit (Full Analysis Set)

Visit	Vehicle (N = 58)	Verkazia QID (N = 56)	Verkazia BID (N = 54)
Baseline	78.4 (16.3)	78.0 (18.2)	80.1 (14.8)
Month 1	-18.3 (21.2)	-33.8 (32.1)	-24.4 (29.6)
Month 2	-18.6 (23.0)	-36.0 (35.5)	-29.1 (27.6)
Month 3	-21.6 (25.1)	-39.8 (34.9)	-35.4 (32.0)
Month 4	-25.4 (26.6)	-44.1 (38.1)	-35.8 (34.9)



[1] Treatment differences (numbers in the middle of the horizontal lines) and 95% confidence intervals (horizonatl lines) are based on ANCOVA model including baseline Itching score and the proportion of time potentially spent in taking study medication as covariate. For subjects that received rescue therapy during the study, all post-rescue data were imputed by the last available data observed prior to rescue initiation.
Note 1: Itching score at each visit was measured using a Visual Analogue Scale (0 = no itch to 100 = maximal itch).

Analyses of the CFS score and Itching score at Month 1 of the efficacy evaluation period in the NOVATIVE Study also provided supporting evidence.

Safety

ADVERSE EVENTS

The most common adverse reactions following the use of Verkazia® were eye pain (12%) and eye pruritis (8%).

WARNINGS & PRECAUTIONS

To avoid the potential for eye injury or contamination, advise patients not to touch the vial tip to the eye or other surfaces.

CONTRAINDICATIONS

None

Clinical Pharmacology

MECHANISMS OF ACTION

Cyclosporine is a calcineurin inhibitor immunosuppressant agent when administered systemically. Following ocular administration, cyclosporine is thought to act by blocking the release of pro-inflammatory cytokines such as IL-2. The exact mechanism of action in the treatment of VKC is not known.

Dose & Administration

ADULTS

Instill one drop of Verkazia®, 4 times daily (morning, noon, afternoon, and evening) in each affected eye.

PEDIATRICS

Children ≥4 years and Adolescents: Ophthalmic: Instill 1 drop in affected eye(s) 4 times daily until signs/symptoms resolve. Treatment may be reinitiated if there is a recurrence.

GERIATRICS

The safety and effectiveness of Verkazia® have not been studied in geriatric patients.

RENAL IMPAIRMENT

There are no dosage adjustments provided in the manufacturer's labeling; however, dosage adjustment unlikely necessary due to low systemic absorption.

HEPATIC IMPAIRMENT

There are no dosage adjustments provided in the manufacturer's labeling; however, dosage adjustment unlikely necessary due to low systemic absorption.

Product Availability

DOSAGE FORM(S) & STRENGTH(S)

Ophthalmic emulsion: 0.1% (1 mg/mL) cyclosporine.