# Understanding Keratoconjunctivitis Sicca (KCS)


NEW
B.I.D.
Restasis™
(Cyclosporine Ophthalmic Emulsion) 0.05%

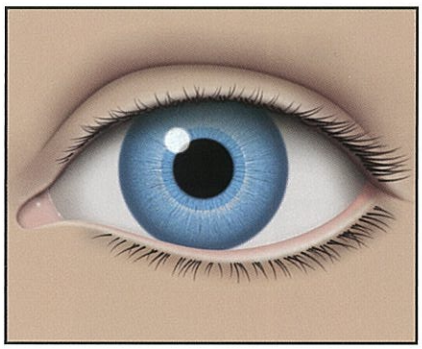
# UNDERSTANDING KERATOCONJUNCTIVITIS SICCA (KCS)

## WHAT IS KCS?

Keratoconjunctivitis sicca, or KCS (also known as dry eye disease), is an immune-based inflammatory pathology of the ocular surface and lacrimal glands that affects 4.3 million Americans (Schein et al, 1997). Depending on the duration and severity of the disease, damage to the ocular surface may be present. Furthermore, patients with chronic, uncontrolled disease have an increased risk of ocular infections (Lemp and Chacko, 1997; Lubniewski and Nelson, 1990).

- The disease is characterized by an abnormality of tear film components that causes the tear film to become unstable.
- The rapid breakup of tear film caused by this instability leads to the appearance of dry spots on the corneal epithelium and resultant patient symptoms including:
  - Dryness
  - Itching
  - Blurred vision
  - Photophobia

## WHAT IS OCULAR HOMEOSTASIS?

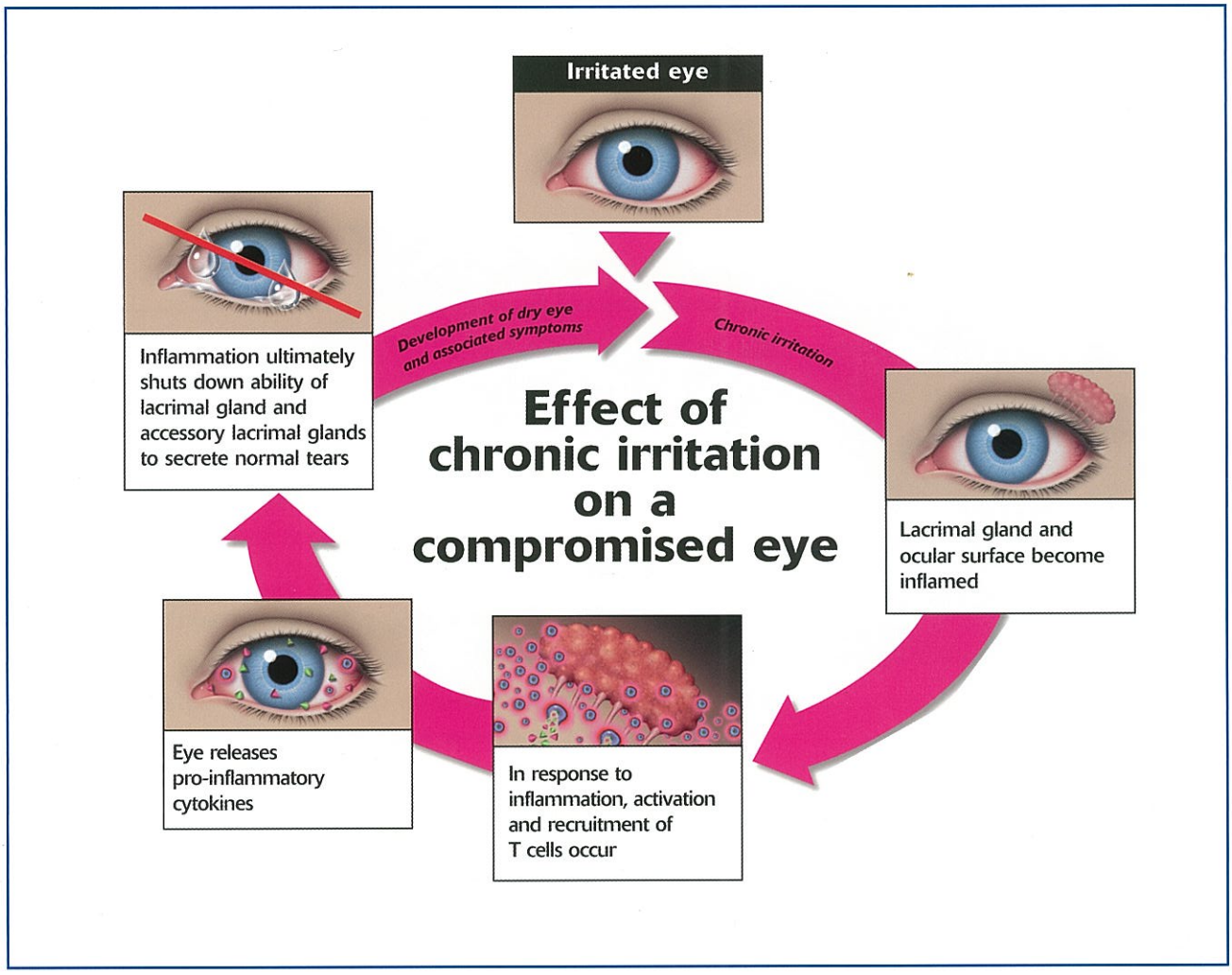


- In the normal eye, the ocular surface and lacrimal glands are connected by a feedback loop, effectively comprising a single functional unit for the maintenance of ocular surface homeostasis.
- The aqueous tears produced by the lacrimal glands lubricate and support the ocular surface, which in turn sends information that can influence tear production back to the lacrimal glands via autonomic neural pathways.
- Any ocular surface irritation triggers increased secretion of ocular surface supportive tears.
- These tears protect and restore (or calm) the ocular surface. No longer irritated, the eye is maintained in a normal, healthy state.

## WHAT IS IMMUNE-BASED INFLAMMATION?

Inflammation is an underlying cause of dry eye disease:

- Dry eye disease is associated with active T cells that migrate into the eye, which can then recruit additional T cells.
- Epithelial cell function is disrupted, interfering with mucin production and decreasing corneal sensitivity.
- This immune-based inflammation shuts down the ability of the lacrimal gland to secrete normal tears, leading to the development of KCS and associated symptoms.
- Chronic irritation causes further inflammation of the lacrimal gland and cornea.



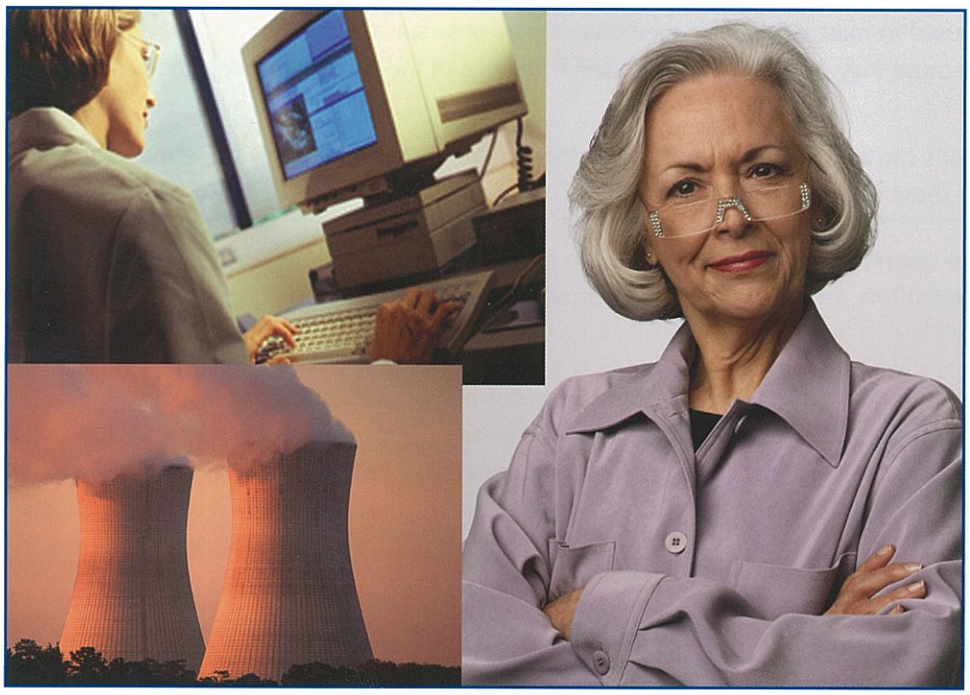
## WHAT ARE THE INCIDENCE AND PREVALENCE OF KCS?

- Demographic studies indicate that dry eye disease affects 4.3 million Americans (Schein et al, 1997)—up to 11% of individuals 30 to 60 years of age (Bjerrum, 1997) and more than 14% of individuals 65 years and older (Schein et al, 1997). Estimates indicate that more than 1 million people suffer with the chronic condition of KCS.
- KCS can affect both men and women, but patients who are most susceptible are postmenopausal women and those with autoimmune diseases.

## WHAT IS THE ETIOLOGY OF KCS?

KCS has multiple etiologies, all of which can result in an immune-based inflammation of the lacrimal glands and ocular surface. Two distinct mechanisms can trigger this response:

- Physical irritation to the ocular surface may occur without predisposing immunoreactivity:
  - Age- or disease-related changes in tear composition or quantity
  - Hormonal changes associated with aging, including menopause
  - Long-term exposure to environmental factors (eg, low humidity, wind, pollutants, and toxic chemicals)
  - Certain medications (eg, ophthalmic medications with preservatives and systemic medications intended to block neural impulses)
- Autoimmune disease can affect the ocular tissues, often in patients who have a genetic or hormonal predisposition to KCS, including:
  - Patients with Sjögren's syndrome, rheumatoid arthritis, scleroderma, or systemic lupus erythematosus
  - KCS secondary to diabetes, thyroid abnormalities, and asthma



## WHAT ROLE DO AGING AND HORMONES PLAY IN THE ETIOLOGY OF KCS?

Current research has revealed that changing hormone levels associated with aging (especially androgen levels) may play a key role in the inflammatory cycle that characterizes dry eye disease. For example, androgen deficiency has been shown to be a critical etiologic factor in the pathogenesis and gender-related incidence of chronic dry eye disease.

- When androgen production decreases due to aging (around the same time as menopause), the androgen level in women falls below a protective anti-inflammatory threshold.
- The primary reason that dry eye disease is thought to occur more often in women is that women have lower baseline androgen levels than men.
- Although the decrease of androgen levels in men may be quantitatively the same, the effects of the decrease are not as great because baseline levels of androgen are higher in males.

## WHAT ROLE DO ENVIRONMENTAL FACTORS PLAY IN THE ETIOLOGY OF KCS?

One of the most obvious environmental factors involved with the pathogenesis of dry eye disease is prolonged exposure to a harsh environment in which low humidity, wind, and pollutants combine to cause inflammation of the ocular surface. The use of heaters and air conditioners has been implicated as well.

## WHAT ROLE DO MEDICATIONS PLAY IN THE ETIOLOGY OF KCS?

Both topical and systemic medications can also exacerbate the development of dry eye disease:

- Chronic use of topical glaucoma medications, particularly the older types such as pilocarpine or epinephrine, can cause lymphocytic infiltration and inflammation of the conjunctiva that result in dry eye.
- The preservatives used in most ophthalmic medications may pose special problems for individuals at risk for dry eye disease because they disrupt the compositional balance of the natural tear film and can be toxic to epithelial cells.
- Systemic medications can also contribute to the development of dry eye, especially those that block neural impulses. Some of these medications include:
  - Antidepressants
  - Antihistamines
  - Antihypertensives
  - Beta-blockers
  - Decongestants
  - Diuretics
  - Oral contraceptives
  - Tranquilizers
  - Ulcer medications

## WHAT ROLE DO SYSTEMIC CONDITIONS PLAY IN THE ETIOLOGY OF KCS?

KCS may also be secondary to many systemic conditions such as diabetes, thyroid abnormalities, and asthma. Particularly important in this regard are autoimmmune disorders such as Sjögren's syndrome, rheumatoid arthritis, and lupus. Of these, the one of greatest consequence is Sjögren's syndrome—a chronic, inflammatory condition that affects multiple body systems and occurs predominantly in women.

## HOW IS KCS DIAGNOSED?

The objectives of diagnosing and managing patients with KCS include (AAO, 1998):

- Preservation of vision
- Prevention or minimization of structural damage to the ocular surface
- Improvement of patient comfort

A reliable diagnosis should include consideration of multiple signs and symptoms of ocular irritation as well as problems not related to tear film, followed by an assessment of tear film stability.

- If tear film instability is established, a distinction must be made between aqueous tear deficiency and meibomian gland disease.
- If tear film instability is due to aqueous tear deficiency, further differentiation of Sjögren's syndrome from non-Sjögren's syndrome is required (Pflugfelder et al, 1998).

Specific steps in the diagnostic process include (AAO, 1998):

| History of Present Illness | Ocular History | Medical History | Physical Examination | Additional Tests |
|---|---|---|---|---|
| ■ Signs and symptoms<br>■ Exacerbating conditions<br>■ Prolonged visual efforts associated with a decreased blink rate<br>■ Duration of symptoms<br>■ Use of topical medications<br>■ Use of artificial tears | ■ Present or prior contact lens use<br>■ Allergic conjunctivitis<br>■ Eyelid surgery<br>■ Bell's palsy<br>■ Chronic ocular surface inflammation | ■ Age<br>■ Presence or absence of relevant, concomitant dermatological disease<br>■ Atopy<br>■ Menopause<br>■ Trauma<br>■ Autoimmune disease<br>■ HIV infection<br>■ Use of systemic medications | ■ Visual acuity<br>■ External examination<br>■ Slit-lamp examination | ■ Tear breakup time (TBUT)<br>■ Staining (fluorescein, rose bengal, lissamine green)<br>■ Schirmer test (with or without anesthesia)<br>■ Ocular Surface Disease Index® (OSDI®) |

## HOW IS KCS MANAGED?

Historically, the goal of therapy for KCS has focused on relief of symptoms (via protection of the cornea and conjunctiva from epithelial breakdown), enhancement of tear film stability, and prevention of ocular surface damage.

Today, however, these goals are changing to focus on modification and elimination of precipitating factors and treatment of the underlying condition as well as on symptomatic relief. Equally critical is appropriate management of patient expectations. This is because therapeutic outcomes are at least partially dependent on patient compliance, which in turn is dependent on the patient's knowledge and understanding about his or her condition.

## WHAT PHARMACOLOGICAL TREATMENTS ARE AVAILABLE FOR THE MANAGEMENT OF KCS?

Although there are several traditional treatments available for treating KCS, they are universally palliative, treating only the symptoms and having significant limitations. Tear substitutes, or ocular lubricants, are intended to supplement natural tears; however, they offer only short-term relief and must be instilled frequently throughout the day. Furthermore, excessive use of preserved tear substitutes by patients with more severe KCS may exacerbate an already compromised ocular surface.

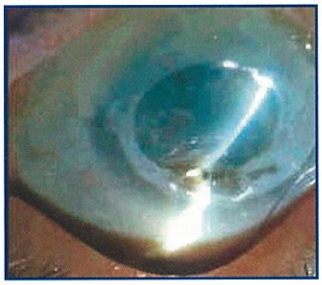
Ocular lubricants are formulated to optimize the physical and chemical characteristics of the tear film. Examples of ocular lubricants include:

- Drops
- Ointments
- Inserts
- Preservative-free, unit-dose products

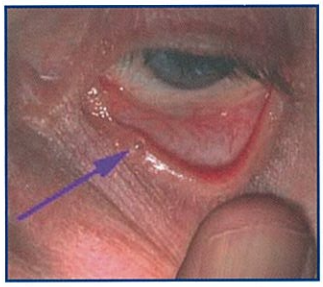
The ideal ocular lubricant should create a stable tear film; should be comfortable, sterile, and nontoxic; should be neutral or slightly acidic; and should be characterized by a long retention time. Additionally, the lubricant should not impair ocular tissue regeneration, and its adhesion tension should be as close as possible to that of normal tears. Finally, the viscosity of an ocular lubricant should not be so high that it impairs lubrication, blurs vision, or causes crusting.

## WHAT OTHER FORMS OF MEDICAL MANAGEMENT ARE AVAILABLE FOR THE SYMPTOMS OF KCS?

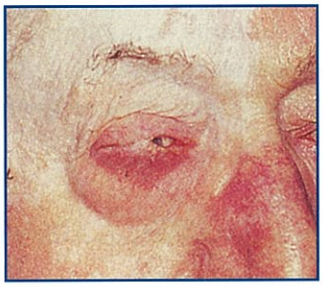
- Moist chamber goggles provide temporary relief by protecting the eye from the outside environment.
- Bandage contact lenses cover filaments, thereby reducing the friction and pain caused by blinking.
- Punctal occlusion effectively reduces the outflow and drainage of tears.
- Lateral tarsorrhaphy, in which the lateral third of the upper lid is sutured to the lateral third of the lower lid, provides physical protection and helps decrease tear evaporation.
- Cautery of the puncta and argon laser punctoplasty are used for permanent punctal occlusion, and lid surgery can correct congenital or acquired lid abnormalities that cause chronic dry eye disease (Lubniewski and Nelson, 1990).



*Bandage contact lenses*



*Punctal inserts*



*Lateral tarsorrhaphy*

## WHAT ARE THE LIMITATIONS OF CURRENT MANAGEMENT OPTIONS FOR THE SYMPTOMS OF KCS?

- The most significant limitation of ocular lubricants for the management of symptoms of KCS is that these products are palliative in nature, providing—at best—limited relief.
- Importantly, the use of contact lenses for vision correction in KCS patients is discouraged because the use of contact lenses will tend to increase not only the risk of infection, but also the rate of tear evaporation.
- Although some patients benefit from punctal occlusion, many others do not—even if the quantity of tears on the ocular surface increases.
  - Clinical experience suggests that punctal occlusion may actually decrease tear production, clearance, and ocular surface sensation (Yee et al, 1999).
- Lateral tarsorrhaphy is a clinically effective treatment option, but most patients consider it to be cosmetically unacceptable and it is performed in only the most severe cases of KCS.

## IS THERE A PRESCRIPTION THERAPEUTIC OPTION FOR THE MANAGEMENT OF KCS?

RESTASIS™ (Cyclosporine Ophthalmic Emulsion) 0.05% contains the active ingredient cyclosporine, a topical immunomodulator with anti-inflammatory effects. Previously used as a systemic agent for the prevention of organ transplant rejection, cyclosporine has also been used systemically in the treatment of psoriasis and rheumatoid arthritis. Because KCS is the result of an immune-based inflammatory process, cyclosporine has been investigated as a therapeutic treatment for dry eye disease.

## WHAT ARE THE BENEFITS OF RESTASIS™?

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

RESTASIS™ is the first and only prescription therapy to improve tear deficiency due to ocular inflammation in patients with KCS by treating an underlying cause of KCS—immune-based inflammation. It is distinct from other treatments that provide only temporary, palliative relief from the symptoms of KCS. RESTASIS™ ophthalmic emulsion offers the only therapeutic alternative to punctal occlusion, moist chamber goggles, surgery, and certain topical medications and is the only proven therapeutic agent for treating the underlying inflammation associated with KCS.

RESTASIS™ is thought to act through 2 important modes of action—immunomodulation and suppression of inflammation without immunosuppressive effects.

By reducing ocular inflammation, RESTASIS™ increases tear production. Increased tear production, in turn, allows the ocular surface to return to a more normal state. As a result, tear film stabilizes, symptoms of dryness dissipate, and dry eye patients experience increasing relief. This was proven by results of clinical studies (Sall et al, 2000) in which RESTASIS™ ophthalmic emulsion dramatically improved Schirmer Tear Test scores, an accepted methodology by which tear production is assessed. This improvement was shown via 2 independent databases to correlate strongly with decreases in corneal staining, indicating improved corneal integrity, as well as improvement in 4 key symptoms of KCS: dryness, itching, blurred vision, and photophobia. Most importantly, it should be noted that patients continued to experience improvement over the course of therapy.

RESTASIS™ ophthalmic emulsion administered twice daily for up to 12 months was proven safe and well tolerated locally and without significant systemic effects (Small et al, 2002). This favorable safety profile is especially important considering the lack of satisfactory alternative therapies available for KCS patients.

RESTASIS™ represents a valuable new treatment option for healthcare providers and payers, with substantial benefits for KCS patients with tear deficiency due to ocular inflammation.

## REFERENCES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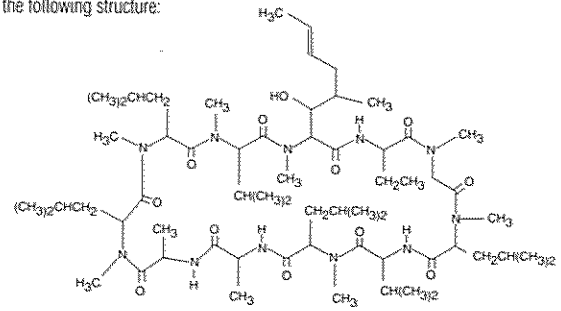
# RESTASIS™

(cyclosporine ophthalmic emulsion) 0.05%
Sterile, Preservative-Free

## DESCRIPTION

RESTASIS™ (cyclosporine ophthalmic emulsion) 0.05% contains a topical immunomodulator with anti-inflammatory effects. Cyclosporine's chemical name is Cyclo[[(*E*)-(2*S*,3*R*,4*R*)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoyl]-L-2-aminobutyryl-*N*-methylglycyl-*N*-methyl-L-leucyl-L-valyl-*N*-methyl-L-leucyl-L-alanyl-D-alanyl-*N*-methyl-L-leucyl-*N*-methyl-L-leucyl-*N*-methyl-L-valyl] and it has the following structure:



Formula: $C_{62}H_{111}N_{11}O_{12}$ Mol. Wt.: 1202.6

Cyclosporine is a fine white powder. RESTASIS™ appears as a white opaque to slightly translucent homogeneous emulsion. It has an osmolality of 230 to 320 mOsmol/kg and a pH of 6.5 to 8.0.

Each mL of RESTASIS™ ophthalmic emulsion contains: **Active:** cyclosporine 0.05%. **Inactives:** glycerin; castor oil; polysorbate 80; carbomer 1342; purified water, and sodium hydroxide to adjust the pH.

## CLINICAL PHARMACOLOGY

### Mechanism of action:

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.

### Pharmacokinetics:

Blood cyclosporin A concentrations were measured using a specific high pressure liquid chromatography-mass spectrometry assay. Blood concentrations of cyclosporine, in all the samples collected, after topical administration of RESTASIS™ 0.05%, BID, in humans for up to 12 months, were below the quantitation limit of 0.1 ng/mL. There was no detectable drug accumulation in blood during 12 months of treatment with RESTASIS™ ophthalmic emulsion.

### Clinical Evaluations:

Four multicenter, randomized, adequate and well-controlled clinical studies were performed in approximately 1200 patients with moderate to severe keratoconjunctivitis sicca. RESTASIS™ demonstrated statistically significant increases in Schirmer wetting of 10 mm versus vehicle at six months in patients whose tear production was presumed to be suppressed due to ocular inflammation. This effect was seen in approximately 15% of RESTASIS™ ophthalmic emulsion treated patients versus approximately 5% of vehicle treated patients. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

No increase in bacterial or fungal ocular infections was reported following administration of RESTASIS™.

## INDICATIONS AND USAGE

RESTASIS™ ophthalmic emulsion is 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.

## CONTRAINDICATIONS

RESTASIS™ is contraindicated in patients with active ocular infections and in patients with known or suspected hypersensitivity to any of the ingredients in the formulation.

## WARNING

RESTASIS™ ophthalmic emulsion has not been studied in patients with a history of herpes keratitis.

## PRECAUTIONS

General: For ophthalmic use only.

### Information for Patients:

The emulsion from one individual single-use vial is to be used immediately after opening for administration to one or both eyes, and the remaining contents should be discarded immediately after administration.

Do not allow the tip of the vial to touch the eye or any surface, as this may contaminate the emulsion.

RESTASIS™ should not be administered while wearing contact lenses. Patients with decreased tear production typically should not wear contact lenses. If contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted 15 minutes following administration of RESTASIS™ ophthalmic emulsion.

### Carcinogenesis, Mutagenesis, and Impairment of Fertility:

Systemic carcinogenicity studies were carried out in male and female mice and rats. In the 78-week oral (diet) mouse study, at doses of 1, 4, and 16 mg/kg/day, evidence of a statistically significant trend was found for lymphocytic lymphomas in females, and the incidence of hepatocellular carcinomas in mid-dose males significantly exceeded the control value.

In the 24-month oral (diet) rat study, conducted at 0.5, 2, and 8 mg/kg/day, pancreatic islet cell adenomas significantly exceeded the control rate in the low dose level. The hepatocellular carcinomas and pancreatic islet cell adenomas were not dose related. The low doses in mice and rats are approximately 1000 and 500 times greater, respectively, than the daily human dose of one drop (28 µL) of 0.05% RESTASIS™ BID into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed.

Cyclosporine has not been found mutagenic/genotoxic in the Ames Test, the V79-HGPRT Test, the micronucleus test in mice and Chinese hamsters, the chromosome-aberration tests in Chinese hamster bone-marrow, the mouse dominant lethal assay, and the DNA-repair test in sperm from treated mice. A study analyzing sister chromatid exchange (SCE) induction by cyclosporine using human lymphocytes *in vitro* gave indication of a positive effect (i.e., induction of SCE).

No impairment in fertility was demonstrated in studies in male and female rats receiving oral doses of cyclosporine up to 15 mg/kg/day (approximately 15,000 times the human daily dose of 0.001 mg/kg/day) for 9 weeks (male) and 2 weeks (female) prior to mating.

### Pregnancy-Teratogenic effects:

Pregnancy category C.

**Teratogenic effects:** No evidence of teratogenicity was observed in rats or rabbits receiving oral doses of cyclosporine up to 300 mg/kg/day during organogenesis. These doses in rats and rabbits are approximately 300,000 times greater than the daily human dose of one drop (28 µl) 0.05% RESTASIS™ BID into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed.

**Non-Teratogenic effects:** Adverse effects were seen in reproduction studies in rats and rabbits only at dose levels toxic to dams. At toxic doses (rats at 30 mg/kg/day and rabbits at 100 mg/kg/day), cyclosporine oral solution, USP, was embryo- and fetotoxic as indicated by increased pre- and postnatal mortality and reduced fetal weight together with related skeletal retardations. These doses are 30,000 and 100,000 times greater, respectively than the daily human dose of one-drop (28 µl) of 0.05% RESTASIS™ BID into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed. No evidence of embryofetal toxicity was observed in rats or rabbits receiving cyclosporine at oral doses up to 17/mg/kg/day or 30 mg/kg/day, respectively, during organogenesis. These doses in rats and rabbits are approximately 17,000 and 30,000 times greater, respectively, than the daily human dose.

Offspring of rats receiving a 45 mg/kg/day oral dose of cyclosporine from Day 15 of pregnancy until Day 21 post partum, a maternally toxic level, exhibited an increase in postnatal mortality; this dose is 45,000 times greater than the daily human topical dose, 0.001 mg/kg/day, assuming that the entire dose is absorbed. No adverse events were observed at oral doses up to 15 mg/kg/day (15,000 times greater than the daily human dose).

There are no adequate and well-controlled studies of RESTASIS™ in pregnant women. RESTASIS™ should be administered to a pregnant woman only if clearly needed.

### Nursing Mothers:

Cyclosporine is known to be excreted in human milk following systemic administration but excretion in human milk after topical treatment has not been investigated. Although blood concentrations are undetectable after topical administration of RESTASIS™ ophthalmic emulsion, caution should be exercised when RESTASIS™ is administered to a nursing woman.

### Pediatric Use:

The safety and efficacy of RESTASIS™ ophthalmic emulsion have not been established in pediatric patients below the age of 16.

### Geriatric Use:

No overall difference in safety or effectiveness has been observed between elderly and younger patients.

## ADVERSE REACTIONS

The most common adverse event following the use of RESTASIS™ was ocular burning (17%).

Other events reported in 1% to 5% of patients included conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).

## DOSAGE AND ADMINISTRATION

Invert the unit dose vial a few times to obtain a uniform, white, opaque emulsion before using. Instill one drop of RESTASIS™ ophthalmic emulsion twice a day in each eye approximately 12 hours apart. RESTASIS™ can be used concomitantly with artificial tears, allowing a 15 minute interval between products. Discard vial immediately after use.

## HOW SUPPLIED

RESTASIS™ ophthalmic emulsion is packaged in single use vials. Each vial contains 0.4 mL fill in a 0.9 mL LDPE vial; 32 vials are packaged in a polypropylene tray with an aluminum peelable lid.

RESTASIS™ 32 Vials 0.4 mL each-NDC 0023-9163-32

Storage: Store RESTASIS™ ophthalmic emulsion at 15° to 25° C (59° to 77° F).
KEEP OUT OF THE REACH OF CHILDREN.

**Rx Only**

ALLERGAN


Irvine, CA 92612, U.S.A.

US PAT 4,649,047; 4,839,342; 5,474,979.