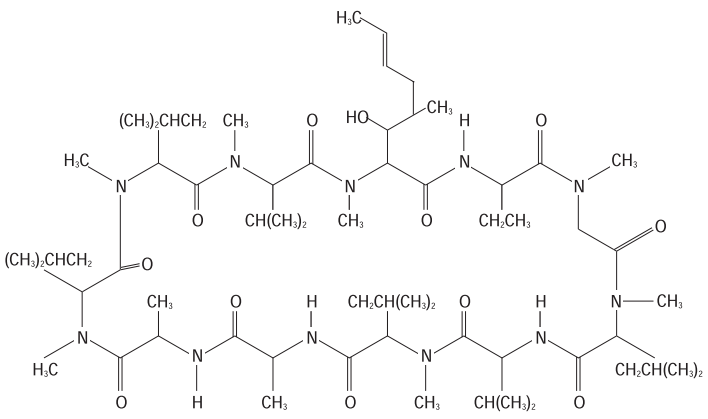
DESCRIPTION

RESTASIS® (cyclosporine ophthalmic emulsion) 0.05% contains a topical immunomodulator with anti-inflammatory effects. Cyclosporine's chemical name is Cyclo[[(E)-(2S,3R,4R)-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:

Structural Formula



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 6.5-8.0.

Each mL of RESTASIS® contains: **Active:** cyclosporine 0.05%. **Inactive:** 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 cyclosporine 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®.

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® 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® 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.

abbvie

5730

20082782

RESTASIS®
Cyclosporine Ophthalmic Emulsion 0.05%
Sterile, Preservative-Free

5730

WARNING

RESTASIS® has not been studied in patients with a history of recurrent 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.

Patients should be advised not to discontinue therapy prematurely.

To avoid contamination or possible eye injury, do not touch the tip of the bottle or vial to any other surface and avoid contact with the eye. 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®.

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 300 and 80 times greater (normalized to body surface area), respectively, than the daily human dose*, or alternatively, 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.

Drug Interactions

No interaction studies have been performed. Drugs that affect the cytochrome P-450 3A may alter cyclosporine metabolism. There is no detectable systemic absorption of Restasis following ocular administration. Therefore no interaction of topically applied Restasis with systemic drugs is expected to occur.

Effects on Ability to Drive and Use Machines

Restasis may cause transient blurring of vision which may impair the ability to drive or operate machines. The patient should wait until their vision has cleared before driving or using machinery.

0120001

Colors:
Black
Keyline

abbvie	**File Upload Date:** 18 Dec 2023 09:59 UTC	**Version Number:** 3	**Artwork is created at 100%**
Brief ID: PROD-2023-001699	**New Control Number:** 20082782	**PDS:** N/A	
Size or Drawing Number: N/A			**LAGN Drawing:** 0120001
Braille Code: N/A	**Packaging Barcode Type:** Code 128C	**Packaging Barcode Number:** 5730	
Variable Data Required: No			
Comments: Total pages: 2 Drop dieline, swatches, and art block before processing. Vendor allowed to add printer marks, as necessary.			

USE IN SPECIFIC POPULATIONS

Pregnancy-Teratogenic effects:

Pregnancy category C.

Teratogenicity :

Cyclosporine was found to be non-teratogenic in appropriate test systems.

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 pregnant women only if clearly needed. Cyclosporine ophthalmic emulsion 0.05% is not detected systemically following topical ocular administration, and maternal use is not expected to result in fetal exposure to the drug. Studies in animals have shown reproductive toxicity only at high maternotoxic doses.

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®, caution should be exercised when RESTASIS® is administered to a nursing woman.

Pediatric Use:

The safety and efficacy of RESTASIS® 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

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The most commonly reported adverse reaction was eye burning reported in approximately 17% of patients in the first year with the incidence of new reports decreasing to 5% at 2 years.

The frequency is defined as follows: Very Common (≥1/10); Common (≥1/100, <1/10); Uncommon (≥1/1,000, <1/100); Rare (≥1/10,000, <1/1,000); Very Rare (<1/10,000).

Nervous system disorders

Common: Headache

Uncommon: Dizziness

Eye disorders

Very common: Eye burning.

Common: Eye irritation, foreign body sensation in eye, ocular / conjunctival hyperaemia, eye pain, eye stinging, eye discharge, photophobia, eye pruritus, visual disturbance (blurred vision), dry eye.

Uncommon: Ulcerative keratitis, eyelid oedema, erythema of eyelid, lacrimation increased.

Gastrointestinal disorders

Uncommon: Nausea

Skin and subcutaneous tissue disorders

Uncommon: Rash

Post-marketing Experience

The following adverse reactions have been identified during post approval use of RESTASIS®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Reported reactions have included:

Eye Disorders

Eye swelling

Immune System Disorders

Hypersensitivity

Rare cases including severe angioedema, face swelling, tongue swelling, pharyngeal edema, and dyspnea

Injury, Poisoning and Procedural Complications

Superficial injury of the eye (from the vial tip touching the eye during administration)

Nervous System Disorders

Burning sensation

Skin and Subcutaneous Tissue Disorders

Pruritus, Urticaria

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® 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.

OVERDOSAGE

Systemic overdose is unlikely to occur after ocular administration of RESTASIS®. Due to low systemic concentrations of cyclosporine after topical treatment with the ophthalmic emulsion, the likelihood of systemic intoxication from topical overdose is remote.

HOW SUPPLIED

RESTASIS® is packaged in single use vials. Each vial contains 0.4 mL fill in a 0.9 mL LDPE vial; The carton containing 30 unit-dose vials will have three sealed pouches (each containing 2 strips of 5 unit-dose vials).

Storage: Store RESTASIS® below 30°C.

KEEP OUT OF REACH OF CHILDREN.

Rx Only

Revised November 2023

abbvie

Manufactured by:

Allergan Sales, LLC

Waco, Texas, U.S.A.

RESTASIS and its design are trademarks of Allergan, Inc., an AbbVie company.

Colors:

Black

Keyline

abbvie	**File Upload Date:** 18 Dec 2023 09:59 UTC	**Version Number:** 3	**Artwork is created at 100%**
Brief ID: PROD-2023-001699	**New Control Number:** 20082782	**PDS:** N/A	
Size or Drawing Number: N/A			**LAGN Drawing:** 0120001
Braille Code: N/A	**Packaging Barcode Type:** Code 128C	**Packaging Barcode Number:** 5730	
Variable Data Required: No			
Comments: Total pages: 2 Drop dieline, swatches, and art block before processing. Vendor allowed to add printer marks, as necessary.			