PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr **RESTASIS®**

Cyclosporine Ophthalmic Emulsion

Emulsion, 0.05% w/v, Ophthalmic

Anti-Inflammatory / Immunomodulator

ATC Code: S01XA18

AbbVie Corporation

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St-Laurent, Quebec

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Date of Initial Authorization:
AUG 19, 2010

Date of Revision:
AUG 4, 2022

Submission Control Number: 266000

RECENT MAJOR LABEL CHANGES

None at the time of the most recent authorization.

TABLE OF CONTENTS

Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

RESTASIS® (cyclosporine) is indicated for:

- the treatment of moderate to moderately severe (Level 2-3 severity by DEWS Guidelines) aqueous deficient dry eye disease, characterized by moderate to moderately severe: ocular staining, reduction in tear production and fluctuating visual symptoms, such as blurred vision.

The efficacy of RESTASIS alone has not been demonstrated in patients with more severe disease (Level 4 DEWS Classification).

1.1 Pediatrics

Pediatrics (<18 year of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (> 65 years of age): No overall difference in safety or effectiveness has been observed between elderly and younger subjects.

2 CONTRAINDICATIONS

- RESTASIS is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- RESTASIS is contraindicated in patients with active ocular infections.

4 DOSAGE AND ADMINISTRATION

4.1 Dosing Considerations

- There are no special dosing considerations which need to be taken into account prior to initiating therapy with RESTASIS.

4.2 Recommended Dose and Dosage Adjustment

- The recommended dose is one drop of RESTASIS, instilled twice a day in each eye approximately 12 hours apart.

This recommended dose is the maximum recommended dose and should be used both as the starting dose and throughout long term treatment. Dosage adjustments should not be necessary based on any co-morbid conditions, given the low systemic availability of the product. Limited data from clinical studies exists for long term administration of RESTASIS (up to 40 months). It is expected that use of the product will continue long term.

Health Canada has not authorized an indication for pediatric use.

4.3 Reconstitution

Not applicable.

4.4 Administration

The vial should be inverted a few times to obtain a uniform, white, opaque emulsion before using.

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 to avoid touching the tip of the vial to the eye or any surface, as this may contaminate the emulsion. To avoid the potential for injury to the eye, patients should also be advised not to touch the vial container to the eye.

RESTASIS should not be administered while the patient is wearing contact lenses. If contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted 15 minutes after the administration of RESTASIS.

RESTASIS may be used concomitantly with artificial tears. The patient should be advised to allow a 15-minute interval between administration of RESTASIS and the artificial tear product.

4.5 Missed Dose

If a dose of this medication is missed, it should be taken as soon as possible. However, if it is almost time for the next dose, the missed dose should be skipped and the regular dosing schedule resumed. Doses should not be doubled. The dose should not exceed two drops in the affected eye(s) daily.

5 OVERDOSAGE

There is no experience with overdose in humans using topical cyclosporine ophthalmic emulsion. Excessive topical use of cyclosporine ophthalmic emulsion would not be expected to contribute to any ocular toxicity. Due to low systemic concentrations of cyclosporine after topical treatment with the ophthalmic emulsion, the likelihood of systemic intoxication from topical overdose is remote.

A single vial of RESTASIS (0.05% cyclosporine emulsion) contains 0.2 mg of cyclosporine. The recommended weight-normalized starting dose of NEORAL® (cyclosporine), which is administered systemically for rheumatoid arthritis and plaque psoriasis, is 2.0 mg/kg/day. Therefore, the dose ingested by drinking the contents of an entire vial by a child weighing 14 kg (30 lb) would be approximately 140 times lower than the recommended starting dose of NEORAL.

For management of a suspected drug overdose, including accidental ingestion, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Ophthalmic	Emulsion, 0.05% w/v	Carbomer Copolymer Type A, castor oil, glycerin, polysorbate 80, purified water and sodium hydroxide.

RESTASIS is available as a sterile preservative-free emulsion supplied in low density polyethylene single use vials containing 0.4 mL each, packaged in trays containing 30 and 60 vials.

7 WARNINGS AND PRECAUTIONS

General

For ophthalmic use only.

Carcinogenesis and Mutagenesis

See 16 NON-CLINICAL TOXICOLOGY.

Driving and Operating Machinery

RESTASIS may cause transient blurred vision due to its emulsion formulation. If patients experience blurred vision, they should be advised not to drive or operate machinery until vision has cleared.

Immune

There is the potential to experience hypersensitivity to RESTASIS. Reactions of severe angioedema, face swelling, tongue swelling, pharyngeal oedema, dyspnea and urticaria have been reported with the use of RESTASIS. See 8.5 Post-Market Adverse Drug Reactions. If an allergic reaction occurs, patients should be advised to discontinue the drug.

Ophthalmologic

RESTASIS has not been studied in patients with a history of herpes keratitis, end stage lacrimal gland disease, keratoconjunctivitis sicca (KCS) secondary to the destruction of conjunctival goblet cells such as occurs with Vitamin A deficiency, or scarring, such as occurs with cicatricial pemphigoid, alkali burns, Stevens-Johnson syndrome, trachoma, or irradiation.

See 4.4 Administration for further information regarding the use of RESTASIS with respect to contamination, eye injury, and contact lens use.

7.1 Special Populations

7.1.1 Pregnant Women

There are no adequate data from the use of RESTASIS in pregnant women. Studies in animals have shown reproductive toxicity at high maternotoxic doses. See 16 NON-CLINICAL TOXICOLOGY.

RESTASIS should not be used during pregnancy unless the benefits outweigh the risks.

7.1.2 Breast-feeding

Cyclosporine is known to be excreted in human milk following systemic administration, but excretion in human milk after topical administration 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.

7.1.3 Pediatrics

Pediatrics (< 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (> 65 years of age): No overall difference in safety or effectiveness has been observed between elderly and younger patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most common adverse reaction following the use of RESTASIS is ocular burning.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

In the combined data from the three key Phase 3 clinical studies, approximately 29% of treated patients experienced treatment-related adverse events (adverse reactions) in the first year. The majority were ocular, mild or moderate in severity, and none were serious. The most commonly reported adverse reaction was eye burning, which was reported in approximately 17% of patients in the first year; the incidence of new reports decreased to 5% at 2 years. The observed adverse drug reactions are provided below for those events observed at an incidence of ≥1% in the three vehicle-controlled clinical trials.

Table 2 – Vehicle Controlled Clinical Trial Treatment-Related Adverse Drug Reactions Reported by ≥ 1% of Patients in the Cyclosporine 0.05% Treatment Group (ITT Population – Month 12 Pooled Data for Studies 192371-002, -003, -501)

	Cyclosporine Ophthalmic Emulsion 0.05% n = 436 (%)	Vehicle/Cyclosporine 0.1%	
		6 month Controlled Phase - Vehicle n =442 (%)	6 month Extension Phase - Cyclosporine 0.1% n = 323 (%)
Eye disorders			
Burning eye	74 (17.0%)	29 (6.6%)	21 (6.5%)
Irritation eye	13 (3.0%)	7 (1.6%)	5 (1.5%)
Foreign body sensation	12 (2.8%)	8 (1.8%)	2 (0.6%)
Hyperaemia conjunctival (NOS)	11 (2.5%)	9 (2.0%)	7 (2.2%)
Pain eye	10 (2.3%)	11 (2.5%)	5 (1.5%)
Stinging eye	10 (2.3%)	9 (2.0%)	7 (2.2%)
Discharge eye	9 (2.1%)	7 (1.6%)	1 (0.3%)
Photophobia	9 (2.1%)	3 (0.7%)	-
Pruritus eye	8 (1.8%)	7 (1.6%)	2 (0.6%)
Visual disturbance	8 (1.8%)	12 (2.7%)	1 (0.3%)
Dry eye	7 (1.6%)	2 (0.5%)	-
Nervous system disorders			
Headache	7 (1.6%)	5 (1.1%)	2 (0.6%)

Note that active events are reported over 12 months; vehicle events are reported for 6 month exposure period.
NOS – not otherwise specified

The frequency of all adverse event reporting was generally highest shortly after initiation of RESTASIS treatment, but lessened as treatment continued.

8.3 Less Common Clinical Trial Adverse Reactions

The observed adverse drug reactions are provided below for those events reported by <1% of patients in the cyclosporine 0.05% treatment group in the three vehicle-controlled clinical trials over 12 months.

Ear and labyrinth disorders: Pain ear

Eye disorders: asthenopia, blepharitis, oedema eyelid, chalazion, corneal abrasion, corneal infiltrates, conjunctival haemorrhage, corneal neovascularisation, eczema eyelid, erythema eyelid, keratitis herpes simplex, keratitis superficial punctate, lacrimation increased, oedema eye, oedema eyelid, ulcer corneal (NOS), ulcerative keratitis, vitreous floaters

Gastrointestinal disorders: dryness oral, nausea, salivary gland enlargement, stomatitis ulcer

Infections and infestations: conjunctivitis bacterial, conjunctivitis (NOS)

Musculoskeletal and connective tissue disorders: arthralgia

Nervous system disorders: dizziness

Respiratory, thoracic and mediastinal disorders: rhinitis, infection sinus

Skin and subcutaneous tissue disorders: rash, alopecia

8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Not applicable.

8.5 Post-Market Adverse Reactions

Post-marketing reactions reported to date have been consistent with the events recorded during the vehicle-controlled clinical trials, with the majority of the reported events being ocular. Adverse reactions detected in post-marketing data but not seen with cyclosporine ophthalmic emulsion, 0.05% in clinical trials include:

Eye disorders: eye swelling

Immune system disorders: dyspnea, face swelling, hypersensitivity including severe angioedema, pharyngeal oedema, tongue swelling

Injury, poisoning and procedural complications: superficial injury of the eye (from the vial touching the eye during administration)

Nervous system disorders: burning sensation

Skin and subcutaneous tissue disorders: pruritus**,** urticaria

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No interaction studies have been performed.

Drugs that affect cytochrome P-450 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.

9.3 Drug-Behavioural Interactions

No formal drug-behavioural interaction studies were conducted with RESTASIS.

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 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 KCS, cyclosporine emulsion is thought to act as a partial immunomodulator. The exact mechanism of action is not known.

Topical use of cyclosporine only exerts a local effect, and its action is termed immunomodulatory.

Immunomodulation:

Topical administration of cyclosporine (0.05% or 0.1%) results in suppression of T-cell activation at an early stage (G0 – G1 transition) and inhibition of pro-inflammatory cytokine secretion within the tissues of the ocular surface (conjunctiva and accessory lacrimal glands). These concentrations are high enough to be effective without apparent local toxicity. At these concentrations, however, cyclosporine does not inhibit the systemic (thymic) ability of the body to respond, via T-cell proliferation/activation, to immune challenges. Only the early stages of T-cell activation and not the lymphocytic effector stages responsible for elimination of intruder cells are suppressed. Challenges to the ocular surface can still be met with T cells as well as B cells, phagocytes and other immune-responsive cells.

Supportive evidence for the immune integrity of the ocular surface is demonstrated by the lack of opportunistic ocular infections found in animals and humans. Thus, topical cyclosporine emulsion is thought to exert its therapeutic ophthalmic effect in part by its local immunomodulating activity rather than any systemic immunosuppressant effect.

Cellular Mechanism of Action:

Historically, cyclosporine has been used systemically to prevent solid organ transplant rejection. Its mechanism of action at the cellular level has been well elucidated. As T cells become activated, a complex is formed within the cytoplasm composed of calcineurin (a calcium and calmodulin dependent serine/threonine phosphatase) and nuclear factor of activated T cells (NF-ATc). The formation of the complex results in a dephosphorylation of NF-ATc that is then able to translocate to the nucleus (NF-ATn) where it binds to a DNA-promoter region and initiates synthesis of several factors including pro-inflammatory cytokines.

Cyclosporine binds to its cytoplasmic receptor, cyclophilin, which is found in the cytoplasm of virtually all epithelial cells. Once this binding occurs, the cyclophilin binds to the calcineurin complex and prevents the dephosphorylation of NF-ATc. The nuclear translocation, and thus the promoter binding, is prevented and the T cell is unable to be activated. It is thought that the reason that it takes a few weeks for cyclosporine to be effective is that it does not deactivate previously activated T cells, but prevents new T-cell activation.

It has also been demonstrated that cyclosporine inhibits activation of NF-κB, a nuclear factor involved in the regulation of immune and pro-inflammatory cytokine response genes, such as TNF, IL-1, IL-2, and IL-8. It prevents the synthesis and/or secretion of several TH1 pro-inflammatory cytokines such as IL-2, IL-6, IFN-γ, IL-8, and TNF-α. It is also known to upregulate secretion of TH2-type anti-inflammatory cytokines, including IL-13. IL-13 is thought to be one of the pivotal proteins involved in regulating TH2 (anti- inflammatory cytokine) production.

Dry-Eye Dog Model:

The cellular mechanisms of chronic KCS and the effect of topical cyclosporine on the treatment of dry eye were evaluated using the dry-eye dog model. Fourteen dogs were divided into three groups. Group 1 (N = 5) received 0.2% cyclosporine emulsion, 1 drop twice daily (BID) in both eyes (OU) for 12 weeks. Group 2 (N = 5) received 0.05% cyclosporine emulsion, 1 drop BID OU for 12 weeks. Group 3 (N = 4) received vehicle, 1 drop BID OU for 12 weeks. After 12 weeks of treatment, no significant improvement was found in dogs on 0.05% cyclosporine and /or vehicle. Thus, following a minimum of one month wash out period, four of the five dogs in 0.05% cyclosporine group and two of the four dogs in vehicle group were switched to 0.2% cyclosporine group for further evaluation of the efficacy of 0.2% cyclosporine. Therefore, the total number of dry eye dogs on 0.2% by the end of the study was 11.

Biomicroscopic evaluation of dry eye dogs prior to cyclosporine treatment showed lusterless ocular surface, highly keratinized, translucent to opaque and vascularized. All dogs exhibited these severe ocular manifestations to some degree.

Evaluation of pre-treatment conjunctival biopsies demonstrated an increased level of lymphocytic infiltration suggesting local immunoreactivity. Tissue sections were stained using the TUNEL (Terminal deoxynucleotidyl Transferase Biotin-dUTP Nick End Labeling) method to detect apoptotic cells. TUNEL evaluation of biopsy specimens revealed positivity in lacrimal acinar cells. These terminally differentiated cells are typically stable. Infiltrating lymphocytes that would normally be apoptotic were instead largely negative of apoptosis indicating activation and accumulation for these cells.

Post treatment (0.2% cyclosporine group) biomicroscopic evaluation at 12 weeks revealed restoration of ocular surface luster (Schirmer Tear Test, 10 out of 11 dry eye dogs treated with 0.2% cyclosporine), an improved demeanor (n=11) and a trend of improvement in the clinical conditions including elimination of corneal keratinization and improved corneal clarity. Two of the five dogs on 0.05% cyclosporine also demonstrated a similar improvement in the clinical aspects. No change was found in the vehicle group.

Histological evaluation of post-treatment biopsies demonstrated reduction of excessive lymphocytic conjunctival and accessory lacrimal gland infiltration (n=5 in 0.2% cyclosporine treated group). No significant improvement was found in the vehicle and 0.05% cyclosporine groups. Additionally, a decrease in the TUNEL positivity in lacrimal acinar epithelial cells was found in the 0.2% cyclosporine post-treatment specimens. The level of lymphocytic apoptosis decreased to a more normal range within the accessory lacrimal gland and conjunctiva.

In three dry eye dogs, an ELISA for TGF-β1 was performed in tear samples before and after treatment (0.2% cyclosporine). The increased levels seen in the pre-treatment samples were decreased by more than one-half in two dogs. There was no change in the remaining dog. This initial TGF-β increase is viewed as an ocular surface response to inflammation/wounding. The decreased level of tear TGF-β1 may reflect an improved or healed ocular surface.

10.2 Pharmacodynamics

The administration of higher concentrations of cyclosporine emulsion was not found to improve the clinical response.

10.3 Pharmacokinetics

Cyclosporine A concentrations were measured in human blood using a sensitive liquid chromatography-mass spectrometry assay following ophthalmic administration of cyclosporine (BID for up to 12 months). Blood concentrations of cyclosporine A were below the lower quantitation limit of 0.1 ng/mL. These levels are more than 6550 times lower than those measured during systemic cyclosporine treatment for non-life-threatening indications. There was no detectable drug accumulation in blood during 12 months of treatment with cyclosporine ophthalmic emulsion.

Blood samples collected during Phase 2 and Phase 3 studies of cyclosporine ophthalmic emulsions have shown that blood concentrations are barely detectable and are several orders of magnitude below those produced by approved systemic cyclosporine treatments for rheumatoid arthritis and psoriasis.

Blood cyclosporine A concentrations were determined in a safety, tolerability, and efficacy study of cyclosporine in 162 human patients with moderate to severe dry eye. Male and female patients instilled one ~28.5 µL eyedrop of vehicle emulsion or 0.05, 0.1, 0.2 or 0.4% cyclosporine emulsion twice-daily to each eye for 12 weeks in a double-masked, randomized, parallel-group study.

In each treatment group, blood samples were collected from 28-33 patients at morning troughs (C_{min}) after 1, 4 and 12 weeks of dosing. Blood samples were also collected from approximately 18 patients at 1, 2 and 4 hours after the last dose of the 12-week treatment period. Blood cyclosporine A concentrations were measured using a sensitive and selective LC/MS-MS assay with a quantitation limit of 0.1 ng/mL. C_{max} was defined as the highest concentration observed at 1, 2, or 4 hours after dosing on week 12.

Table 3 – Trough and maximum concentrations of cyclosporine A in human blood after ophthalmic administration of 0.05, 0.1, 0.2 or 0.4% cyclosporine emulsion twice-daily to each eye for 12 weeks.

Cyclosporine emulsion	C_{min} (ng/mL)[a]	C_{max} (ng/mL)[b]
0.05%	<0.1[c]	<0.1[c]
0.1%	<0.1 to 0.102	<0.1[c]
0.2%	<0.1 to 0.108	<0.1 to 0.144
0.4%	<0.1 to 0.157	<0.1 to 0.158

[a] trough concentrations for 28-33 patients per treatment group over 12 weeks of dosing
[b] N=3-5 patients per treatment group after 12 weeks of dosing
[c] below the limit of quantitation

Week 12 blood C_{min} and C_{max} pharmacokinetic parameters are summarized in

Table 3. Cyclosporine A was not detectable in the blood of vehicle-treated patients or during prestudy qualification. Ophthalmic administration of cyclosporine emulsions up to 0.4% produced blood cyclosporine A concentrations of less than 0.2 ng/mL following twice-daily topical dosing over a 12-week period. Trough blood concentrations in most of the 120 patients were less than 0.1 ng/mL. Only five patients showed quantifiable trough concentrations, and these were all less than 0.160 ng/mL. Comparison of trough blood concentrations for weeks 1, 4, and 12 suggests no substantial

accumulation during the 12 week dosing period. Blood C_{max} ranged from less than 0.1 ng/mL to 0.158 ng/mL. Overall, the results of this study indicate that ocular instillation of 0.05-0.4% cyclosporine emulsion produced very low systemic exposure to cyclosporine A**.**

Blood cyclosporine A concentrations were determined in a safety and efficacy study of cyclosporine ophthalmic emulsions in ~300 patients with moderate to severe dry eye. Male and female patients instilled one eyedrop of vehicle emulsion or 0.05 or 0.1% cyclosporine emulsion twice-daily to each eye for six months in a double-masked, randomized, parallel-group study. After six months of treatment, patients in the 0.05% cyclosporine emulsion treatment group were switched to 0.1% cyclosporine emulsion, after which they continued the BID treatment regimen through 12 months.

Blood samples were collected immediately before the morning dose from 113 patients at 1 month and 94 patients at 6 months, after which the trough blood cyclosporine A concentrations in these samples were measured using a highly sensitive and selective LC/MS-MS assay with a quantitation limit of 0.1 ng/mL.

Trough cyclosporine A concentrations were quantifiable in only six samples from six different patients: three at month 1 and three at month 6. One concentration was 0.299 ng/mL and the other five were $\leq$0.144 ng/mL. Of the three patients whose cyclosporine A concentration was quantifiable at three months, two had a concentration that was below the limit of quantification at 6 months, and one did not provide a 6 month sample. All three patients whose cyclosporine A concentration was quantifiable at 6 months had a 3 month concentration that was below the limit of quantification. All trough concentrations other than these six were below the quantitation limit of 0.1 ng/mL.

Blood concentrations of cyclosporine A were determined over the course of one dosing interval in a Phase 3 safety and efficacy study of cyclosporine ophthalmic emulsions in patients with moderate to severe dry eye. The objective was to quantify the C_{max} and AUC_{0-12} of cyclosporine A in blood during topical ophthalmic treatment with 0.05 and 0.1% cyclosporine emulsions.

Male and female patients instilled one eyedrop of vehicle emulsion or 0.05 or 0.1% cyclosporine emulsion twice-daily to each eye for 6 months in a double-masked, randomized, parallel-group study. At month 6, patients in the vehicle emulsion treatment group began treatment with 0.1% cyclosporine emulsion, while patients already taking 0.05 or 0.1% cyclosporine emulsion continued treatment without change. Blood samples were collected during months 9 to 12 from 26 patients at 1, 2, 3, 4, 6, 8, 10, and 12 hours after the morning dose. Blood cyclosporine A concentrations in these samples were measured using a sensitive and selective LC/MS-MS assay with a quantitation limit of 0.1 ng/mL.

Of 208 postdose blood samples from 26 patients, only 3 samples from 3 different patients contained quantifiable cyclosporine. They were: 0.102 ng/mL at 1 hr, 0.104 ng/mL at 2 hr, and 0.105 ng/mL at 3 hr. One of these three patients had received 0.1% cyclosporine emulsion for 9 to 12 months, while the other two patients received vehicle emulsion for the first 6 months of the study and then 0.1% cyclosporine emulsion for 3 to 6 months prior to blood sampling. Concentrations in the other 205 samples were below the quantitation limit of 0.1 ng/mL.

Special Populations and Conditions

Hepatic Insufficiency: Based on the low systemic availability of cyclosporine administered as ophthalmic emulsion, and as there was no detectable drug accumulation in blood during 12 months of treatment with RESTASIS, no increased risk in patients with impaired hepatic function would be expected to occur following the use of RESTASIS.

Renal Insufficiency: Based on the low systemic availability of cyclosporine administered as ophthalmic emulsion, and as there was no detectable drug accumulation in blood during 12 months of treatment

with RESTASIS, no increased risk in patients with impaired renal function would be expected to occur following the use of RESTASIS.

Preclinical:

Ocular Metabolism

Ocular tissues in albino rabbits do not metabolize cyclosporine. After a single 50 μL eyedrop of 0.2% ^{3}H-cyclosporine emulsion to male and female albino rabbits, no metabolites of cyclosporine were detected in conjunctiva, cornea, sclera, aqueous humor, iris-ciliary body, choroid-retina, or lacrimal gland.

Ocular Absorption, Distribution, and Elimination

Topical ophthalmic administration of cyclosporine emulsions to albino rabbits and beagle dogs produced high concentrations in ocular surface tissues and relatively low concentrations in internal ocular tissues. Surface tissue concentrations after ophthalmic instillation of 0.2% cyclosporine emulsion were generally consistent between studies within a given species, and in cornea and sclera were higher in rabbits than beagle dogs after acute administration. Conjunctival concentrations were about equal in rabbits and dogs. Concentrations in internal ocular tissues were low and fairly consistent between studies within a given animal model, and in aqueous humor and iris-ciliary body were higher in albino rabbits than in beagle dogs.

Ocular tissue concentrations of cyclosporine in male beagle dogs given a single 35 μL eyedrop of cyclosporine 0.2% ophthalmic emulsion were also relatively constant from 20 minutes through 3 hours, after which they declined slowly. After a single dose of 0.2% ^{3}H-cyclosporine emulsion, mean (C_{max}) in male beagle dogs was 1,494 ng-eq/g in conjunctiva, 311 ng-eq/g in cornea, 94.6 ng-eq/g in sclera, 0.15 ng-eq/mL in aqueous humor, and 11.2 ng-eq/g in iris-ciliary body.

Ocular tissue concentrations after ophthalmic administration of cyclosporine emulsion to albino rabbits are dose-dependent at formulation concentrations of 0.05% to 0.4%. Cyclosporine emulsions with globule diameters larger than ~50 μm have higher ocular bioavailability than emulsions with globule diameters smaller than ~10 μm, but are physically unstable. Ocular tissue concentrations of cyclosporine in albino rabbits given a 50 μL eyedrop of cyclosporine 0.05% or 0.1% ophthalmic emulsion to each eye BID for 9 1/2 days were relatively consistent through 12 hours after the last dose, and then declined slowly thereafter. After the last dose of 0.05% ^{3}H-cyclosporine emulsion, mean C_{max} in albino rabbits was 643 ng/g in conjunctiva, 1550 ng/g in cornea, 84.5 ng/g in sclera, 1.44 ng/mL in aqueous humor, and 74.7 ng/g in iris-ciliary body. After the last dose of 0.1% ^{3}H-cyclosporine emulsion, mean C_{max} in albino rabbits was 1970 ng/g in conjunctiva, 4810 ng/g in cornea, 262 ng/g in sclera, 7.19 ng/mL in aqueous humor, and 246 ng/g in iris-ciliary body.

Maximal concentrations obtained from rabbit and dog studies indicate that the great majority of drug contained in ocular tissues resides in the outer layers of the eye, and that little penetrates to the interior tissues. High concentrations in ocular surface tissues relative to internal ocular tissues, and long half-lives in ocular surface and internal tissues, suggest that these tissues act as a reservoir for cyclosporine, sequestering cyclosporine and releasing it slowly over prolonged periods. Half-lives in conjunctiva, cornea and sclera after multiple ophthalmic doses to albino rabbits and beagle dogs were longer than 24 hours. Because half-lives are long, peak-to-trough fluctuations in ocular concentrations are small within one dosing interval, thus ensuring continuous exposure to cyclosporine in the ocular surface tissues associated with dry eye.

Cyclosporine does not bind to melanin. Mean iris-ciliary body C_{max} after a single ophthalmic dose of 0.2% cyclosporine emulsion was 63.5 ng/g in albino rabbits and 11.2 ng-eq/g in beagle dogs. Although there were differences between the drop sizes used in rabbit (50 μL) and dog (35 μL) pharmacokinetic studies, tissue concentrations between these 2 species were comparable and in fact tended to be lower in the pigmented species. During BID dosing to dogs for 1 week, mean C_{max} in iris-ciliary body and choroid-retina increased only 219% and 77%, respectively, which further indicates an absence of significant melanin binding in these animals. Because of the lack of substantial accumulation in dog iris-ciliary body and choroid-retina, melanin binding is unlikely in pigmented animals or humans.

11 STORAGE, STABILITY AND DISPOSAL

RESTASIS should be stored between 15 to 25°C. Patients should be instructed to keep unused vials within the resealable tray.

12 SPECIAL HANDLING INSTRUCTIONS

Patients should be advised to avoid touching the tip of the vial to the eye or any surface, as this may contaminate the emulsion. Refer to 4.4 Administration for more detailed information.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

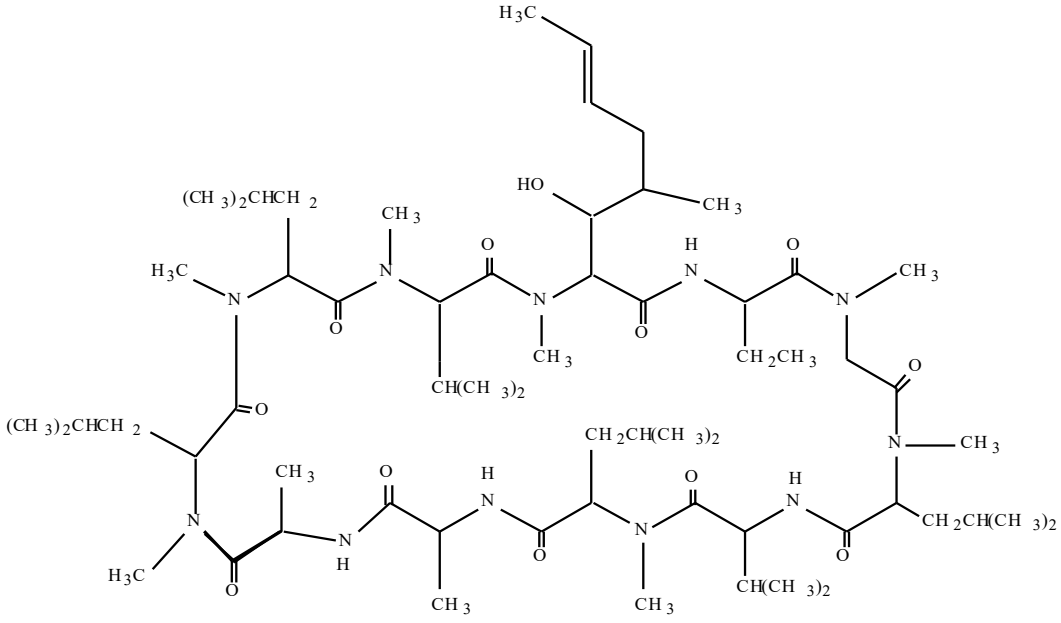
Drug Substance

Proper name: Cyclosporine

Chemical name: 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]

Molecular formula and molecular mass: $C_{62}H_{111}N_{11}O_{12}$ and 1202.6 g/mol

Structural formula:



Physicochemical properties: Cyclosporine is a fine white or almost white powder, practically insoluble in water. Its melting point is 148-151°C.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Moderate to Severe Keratoconjunctivitis Sicca

Table 4 – Summary of patient demographics for clinical trials in patients with moderate to severe keratoconjunctivitis sicca

Study #	Study Design	Dosage, Route of Administration, and Duration[1]	Study Subjects in ITT Population (n)	Mean Age (range)	Gender, # M/F (%)
002	Multicenter, double masked, randomized, vehicle-controlled, parallel-group	0.05%, 0.1% cyclosporine, or vehicle twice daily 12 months (6-month vehicle controlled & 6-month cyclosporine treatment extension)	405	59.3 (21.6 – 90.3)	87 / 318 (21.5 / 78.5)
003	Multicenter, double masked, randomized, vehicle	0.05%, 0.1% cyclosporine, or vehicle twice daily 12 months (6-month vehicle controlled & 6-month cyclosporine treatment extension)	472	59.8 (24.0 – 90.3)	75 / 397 (15.9 / 84.1)
501	Multicenter, double masked, randomized, vehicle	0.05%, 0.1% cyclosporine, or vehicle twice daily 24 months (6-month vehicle controlled & 18-month cyclosporine treatment extension)	438	56.8 (18.4 – 88.3)	66 / 372 (15.1 / 84.9)

[1] In all studies, vehicle patients were switched to 0.1% cyclosporine for the treatment extension period

Details on the patient demographics for the three key vehicle-controlled studies conducted in patients with moderate to severe KCS are provided in **Table 4**. All studies were conducted with cyclosporine emulsion administered via the ophthalmic route on a twice daily schedule. In these Phase 3 studies, 1315 patients with moderate to severe KCS were included in the ITT population. Patient age ranged from 18.4 to 90.3 years, with a mean age ($\pm$ SD) across studies of 58.6 $\pm$ 14.0 years. There were more women (82.7%, 1087/1315) than men (17.3%, 228/1315) and the study population was primarily Caucasian (88.2%, 1160/1315).

In these studies, after an initial masked treatment phase of 6 months duration, all patients were eligible to continue on cyclosporine therapy (those allocated to vehicle in the initial treatment phase were switched to cyclosporine 0.1% in a masked manner).

The study design for all three studies comprised a 2-week run-in phase, when patients were instructed to stop using their concurrently used KCS medication and use only REFRESH® in both eyes as needed. Those patients still meeting the strict entry criteria at this point entered a 6-month vehicle-controlled masked treatment phase. In this phase, patients were randomly assigned to 0.05% or 0.1% cyclosporine or their common vehicle (containing 1.25% castor oil), 1 drop in each eye twice daily for 6 months.

REFRESH use could continue during this treatment phase. However, patients were asked to discontinue REFRESH use 1 week before the Month 4 visit and to try to restrict REFRESH usage subsequent to this visit for the remainder of the trial to less than 8 times daily. Visits and evaluations during the masked treatment phase were made at baseline, and at Months 1, 3, 4 and 6.

Although many findings in each of the individual clinical trials showed numerical superiority for cyclosporine over vehicle, the relatively large standard deviations encountered meant that statistical significance was not usually demonstrated. As the three key studies were identical in design and similar in the study inclusion/exclusion criteria, a *post hoc* meta-analysis was planned and conducted.

The meta-analysis evaluated efficacy in a subpopulation of the three key studies characterized as having Level 2 – Level 3 dry eye disease. This classification was based on the Dry Eye Workshop (DEWS) guidelines (2007), and focused on the population most likely to benefit from therapy with cyclosporine 0.05%, as it was realized after the trials began that severe cases (Level 4 of the DEWS Classification) may not be improved with cyclosporine alone. The Level 2-3 population was comprised of the subset of the ITT population with all of the following baseline scores:

- corneal staining score of 2-4 and
- total staining score of 5-9 and
- Schirmer's with anesthesia score > 2 mm/5 min and
- blurred vision score ≤ 2

The co-primary endpoints for the meta-analysis were absence of total ocular surface staining (cornea plus conjunctiva) and absence of blurred vision at Month 6. The secondary efficacy endpoint was Schirmer's with anesthesia responders. In the latter, a responder was defined as a patient with an increase from baseline ≥ 10 mm/5 min at Month 6 (Month 6 minus baseline).

Table 5 – Summary of patient demographics for pooled analysis in patients with Level 2- 3 dry eye disease (cyclosporine 0.05% and vehicle only)

Study #	Trial Design	Dosage, Route of Administration, and Duration	Study Subjects in ITT Level 2-3 Population[1]	Mean Age (range)[1]	Gender, # M/F (%)[1]
002/003/501	Multicenter, double masked, randomized, vehicle-controlled, parallel-group	0.05%, 0.1% cyclosporine, or vehicle twice daily 6 month vehicle controlled phase	316	60.6 (25– 90)	67 / 249 (21.2 / 78.8)
[1] Includes only those patients who received cyclosporine 0.05% or vehicle only					

At Month 6, depending on the endpoint, the difference in proportion of responders between the cyclosporine and vehicle groups ranged from approximately 9 – 12% (see Table 6).

Table 6 – Results for ITT Level 2-3 patients at Month 6

Study #	Endpoint	Proportion of Patients with a Score of 0 (N)		P value Relative Risk [95% CI]
		Cyclosporine 0.05%	Vehicle	
002/003/501	Primary			
	Total Staining Responder	12.0% (17/142)	3.1% (5/160)	0.003 3.8 [1.46, 9.89]
	Blurred Vision Responders	49.6% (70/141)	37.7% (60/159)	0.036 1.32 [1.02, 1.71]
	Secondary			
	Schirmer's with Anesthesia Responders	17.1% (22/129)	6.2% (9/146)	0.005 2.68 [1.30, 5.52]

Total Staining Responders: A complete staining responder was defined as a patient with Total Staining = 0 at the Month 6 evaluation.

The distribution of total staining scores at baseline in the pooled studies (002/003/501) was similar in the cyclosporine 0.05% and vehicle groups (p = 0.678). The mean total staining score at baseline for each of the two treatment groups was 6.4.

A statistically significantly greater proportion of patients in the cyclosporine 0.05% group were total staining responders compared to the vehicle group at Month 6 (12.0% vs. 3.1%; p = 0.003)

Blurred Vision Responders: A complete blurred vision responder was defined as a patient with blurred vision = 0 at the Month 6 evaluation. As patients did not require blurred vision for entry, a responder

could include those patients whose blurred vision resolved or who had not developed blurred vision at Month 6.

The distribution of blurred vision scores at baseline in the 3 pooled studies was similar in the cyclosporine 0.05% and vehicle groups (p = 0.868). The percentages of patients with blurred vision scores at baseline of 2, 1, and 0 were 43.2%, 26.4%, and 30.4%, respectively, for the cyclosporine 0.05% group and 46.4%, 21.4%, and 32.1%, respectively, for the vehicle group.

A statistically significantly greater proportion of patients in the cyclosporine 0.05% group were blurred vision responders compared to the vehicle group at Month 6 (49.6% vs. 37.7%; p = 0.036)

Schirmer's with Anesthesia Score Responders: A complete responder was defined as a patient with an increase from baseline of ≥10 mm/5 min at Month 6 (Month 6 minus baseline).

The Schirmer's with anesthesia score at baseline in the pooled studies was similar in the cyclosporine 0.05% and vehicle groups (p = 0.494). Mean Schirmer's with anesthesia score at baseline was 6.2 for the cyclosporine 0.05% group and 6.5 for the vehicle treatment group.

A statistically significantly greater proportion of patients in the cyclosporine 0.05% group were Schirmer's with anesthesia responders compared to the vehicle group at Month 6 (17.1% vs. 6.2%; p = 0.005).

The results of the meta-analysis of the three key clinical studies consistently demonstrated statistically significant differences at Month 6 favoring cyclosporine 0.05% for the two co-primary endpoints: the proportion of patients with complete resolution of their total ocular surface staining and the proportion of patients not reporting blurred vision. These results are supported by statistically significant differences in the proportion of patients with a marked improvement in tear production, the key secondary endpoint.

Analysis by Underlying Disease (with/without Sjogren's Syndrome): The subgroup analysis by underlying disease of the Level 2-3 severity population from the three key studies demonstrated that treatment with cyclosporine 0.05% had greater benefits in patients with Sjogren's syndrome compared to vehicle (Total Staining Responders: 17.1% (7/41) vs. 0% (0/34), respectively; p = 0.014). An improvement in total staining responders was observed in patients without Sjogren's Syndrome, however, the difference between cyclosporine 0.05% and vehicle was less and not statistically significant (9.9% (10/101) vs. 4.0% (5/126), respectively; p = 0.072).

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology: Three preclinical safety studies evaluated the local and systemic effects of repeated dose cyclosporine ophthalmic emulsion. The most sensitive species for ocular reactions, the New Zealand White (NZW) rabbit was used in two studies. A species with pigmented eyes, the dog, was used in one additional study.

The animal safety studies used an exaggerated design with cyclosporine emulsion in concentrations up to 0.4% administered as one drop in one eye up to six times daily. This is 12 times the recommended dose, cyclosporine emulsion administered as one drop in each eye twice daily. The dogs and the rabbits (which are approximately seven to 20 times smaller in body weight, respectively, when

compared to a 60 kg human) were exposed systemically with high ocular dosages in order to evaluate the effect of high systemic exposure and the safety of topically administered cyclosporine.

Ocular Safety:

In the subchronic toxicity study, cyclosporine ophthalmic emulsions (0.05%, 0.2% and 0.4%) were well tolerated locally when administered to rabbits for 3 months. The only treatment-related effects were a transient slight ocular discomfort and transient slight conjunctival hyperemia. There were no compound-related microscopic changes in the eye.

Similarly, in the chronic toxicity studies, cyclosporine ophthalmic emulsions were well tolerated locally when administered to rabbits for 6 months and dogs for 52 weeks. The only treatment-related effects were a transient slight ocular discomfort and transient slight conjunctival hyperemia in the rabbit study. There were no compound-related microscopic changes in the eye.

Systemic Safety:

The data from the 3-month and 6-month studies in rabbits and the 1-year study in dogs showed that ophthalmic administration of cyclosporine emulsion in concentrations up to 0.4% administered as 1 drop in 1 eye up to 6 times daily produced no systemic toxicity. There were no changes in the kidney, which is the target organ of toxicity of systemic cyclosporine, nor were there liver changes. No changes were observed in any organ or tissue including the organs related to the immune system (spleen, thymus, lymph nodes). In addition, no changes in the peripheral blood (white blood cells [WBC] and lymphocytes) were noted.

In organ transplant patients receiving high doses of cyclosporine systemically, rare cases of visual disturbances due to morphological cerebral changes have been observed. However, no neurotoxicity was observed following topical cyclosporine in these animal safety studies. All of the ocular tissues were unaffected.

Blood concentrations of cyclosporine A were consistently low, even with the exaggerated dosing regimens used in these studies. The majority of individual blood concentrations were less than 1.0 ng/mL.

Transient, slight ocular discomfort lasting, in most cases, no more than 30 seconds and, slight conjunctival hyperaemia were observed when cyclosporine at concentrations up to 0.4% was topically administered to rabbits (15/sex/group) up to 6 times daily for 6 months. These findings also occurred in rabbits administered the vehicle alone. Sporadic instances of slight to mild iritis and slight aqueous flare also occurred for cyclosporine-treated eyes primarily during the first week of treatment. The maximum mean blood drug concentrations (C_{max}) following instillation of cyclosporine at doses of 0.05%, 0.2%, or 0.4% TID, and 0.4% 6 times daily were 0.328, 0.997, 0.570, and 1.36 ng/mL, respectively. The highest individual peak blood drug concentration was 3.75 ng/mL and was seen in one rabbit dosed with 0.2% cyclosporine.

Similar ocular findings were observed in a 3-month study in rabbits (10/sex/group) in which cyclosporine at concentrations up to 0.4% was topically administered to rabbits 3 times daily for 3 months. The blood drug concentrations in the low dose group animals treated with 0.05% cyclosporine were generally below the 0.2 ng/mL limit of quantitation in rabbits. The maximum mean blood drug concentrations (C_{max}) following instillation of cyclosporine at doses of 0.2% and 0.4% TID were 1.48 and 0.721 ng/mL, respectively. The highest individual peak blood drug concentration of 8.58 ng/mL was seen in 1 rabbit dosed with 0.2% cyclosporine. The majority of the individual peak blood drug concentrations, however, were less than 1.0 ng/mL.

No treatment-related ocular or systemic toxicity was produced in beagle dogs (6/sex/group) when cyclosporine at concentrations up to 0.4% was instilled topically in the eye up to 6 times daily for 1 year. The maximum mean blood drug concentrations (C_{max}) following instillation of cyclosporine at doses of 0.1% TID, 0.2% TID, and 0.4% 6 times daily were 0.299, 0.459, and 0.675 ng/mL, respectively. The highest individual peak blood drug concentration was less than 1.2 ng/mL. There was no marked systemic drug accumulation.

Carcinogenicity: 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 cyclosporine ophthalmic emulsion 0.05% twice daily into each eye of a 60 kg person (0.001 mg/kg), assuming that the entire dose is absorbed.

Genotoxicity: Cyclosporine has not been found to be 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)

Reproductive and Developmental Toxicology: No evidence of teratogenicity was observed in rats or rabbits receiving oral doses of cyclosporine of 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 of one drop (28 µL) of cyclosporine ophthalmic emulsion 0.05% twice daily into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed.

Adverse effects were seen in reproduction studies in rats 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 times and 100,000 times greater, respectively than the daily human dose of one-drop (28 µL) of cyclosporine ophthalmic emulsion 0.05% twice daily into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed.

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 of up to 15 mg/kg/day (15,000 times greater than the daily human dose).

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrRESTASIS®

Cyclosporine Ophthalmic Emulsion

Read this carefully before you start taking **RESTASIS** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **RESTASIS**.

What is RESTASIS used for?

RESTASIS is used to treat certain patients who have a condition called aqueous deficient dry eye disease. If you have this condition your eyes do not produce enough tears to keep the eyes moist and comfortable. Your healthcare professional will decide if RESTASIS is right for you.

How does RESTASIS work?

RESTASIS contains cyclosporine. Cyclosporine is a medicine that changes your immune system. It reduces inflammation in the eye.

What are the ingredients in RESTASIS?

Medicinal ingredients: cyclosporine

Non-medicinal ingredients: carbomer copolymer type A, castor oil, glycerin, polysorbate 80, purified water and sodium hydroxide.

RESTASIS comes in the following dosage forms:

Ophthalmic emulsion, 0.05% w/v

Do not use RESTASIS if:

- you have an eye infection
- you are allergic to cyclosporine or any of the other ingredients in RESTASIS (see **What are the ingredients in RESTASIS?**).
- you are allergic to any component of the RESTASIS container

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take RESTASIS. Talk about any health conditions or problems you may have, including if you:

- have a history of herpes keratitis (infection of the cornea). RESTASIS has not been tested for use in people with this condition.
- You have been told that you have a condition where you are not producing enough tears (called end stage lacrimal gland disease).
- have dry eyes (also known as keratoconjunctivitis sicca) that are the result of Vitamin A deficiency or scarring (which could occur as a result of a blistering disorder, chemical burns, skin disorders, eye infections, or being exposed to radiation). RESTASIS has not been studied in people with these causes of dry eyes.
- drive or operate machinery. RESTASIS may cause your vision to blur right after you put the drops in. Wait a few minutes until your vision clears before you try to drive or operate a machine.
- are breast feeding a baby. It is not known if cyclosporine passes into breast milk.
- are pregnant or planning to become pregnant.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with RESTASIS:

No drug interaction studies have been performed with RESTASIS. Concomitant use with other eye products should be discussed with your healthcare professional beforehand.

How to take RESTASIS:

- Before using, gently shake the vial by tipping it up and down a few times until the emulsion is white and appears the same throughout the vial.
- Each vial should be used immediately after opening for use to one or both eyes, and the remaining contents discarded after use.
- You should also avoid touching the tip of the vial to the eye or any surface as this may contaminate the emulsion, and touching the eye may cause injury.
- RESTASIS may be used together with artificial tears. Wait 15 minutes between using RESTASIS and the artificial tear product.
- Do not use RESTASIS while you wear contact lenses. If you must wear contact lenses, remove the lenses before applying RESTASIS. Wait for 15 minutes after applying RESTASIS before you put your contact lenses back in.

Usual Dose:

The usual adult dose of RESTASIS is one drop into each affected eye. This dose should be applied twice a day, about 12 hours apart.

Overdose:

If you think you, or a person you are caring for, have taken too much RESTASIS contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

If you miss a dose, take it as soon as possible. However, if it is almost time for the next dose, skip the missed dose and go back to the regular dosing schedule. Do not double your dose.

What are possible side effects from using RESTASIS:

These are not all the possible side effects you may have when taking RESTASIS. If you experience any side effects not listed here, tell your healthcare professional.

Eye Disorders

- burning sensation in the eye
- dry eye
- eye discharge
- eye irritation
- eye itching
- eye pain
- eye redness
- blurred vision
- eye swelling
- feeling of grittiness or having something in the eye
- eye sensitivity to light
- accidental injury to the surface of the eye caused by the tip of bottle touching the eye

Nervous System Disorders

- headache

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
Allergic reactions: difficulty breathing, hives, shortness of breath, tongue swelling, throat swelling, face swelling.			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

RESTASIS should be stored between 15 to 25°C. Keep unused vials within the resealable tray.

Keep out of reach and sight of children.

If you want more information about RESTASIS:

- Talk to your healthcare professional.
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.abbvie.ca, or by calling 1-888-704-8271.

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