PRODUCT MONOGRAPH

[Pr]TEVA-CYCLOSPORINE

Cyclosporine

Ophthalmic Emulsion, 0.05% w/v

Teva Standard

Anti-Inflammatory / Immunomodulator

Teva Canada Limited
30 Novopharm Court
Toronto, ON
M1B 2K9

Date of Preparation:
March 14, 2017

Submission Control No: 190985

Table of Contents

PrTEVA-CYCLOSPORINE

Cyclosporine
Ophthalmic Emulsion, 0.05% w/v

Teva Standard

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

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

INDICATIONS AND CLINICAL USE

TEVA-CYCLOSPORINE ophthalmic emulsion, 0.05% w/v is indicated for the treatment of moderate to moderately severe (Level 2-3 severity by DEWS Guidelines)[1] 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. This indication is based on a pooled analysis of a subpopulation of patients from three pivotal studies (see **CLINICAL TRIALS** for further information).

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

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

Pediatrics (< 18 years of age):
No pediatric data are available.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container. For a complete listing, see the **DOSAGE FORMS, COMPOSITION AND PACKAGING** section of the product monograph.

[1] Report of the International Dry Eye WorkShop (DEWS). The Ocular Surface, April 2007; 5(2): 65-204

- Patients with active ocular infections

WARNINGS AND PRECAUTIONS

General
For ophthalmic use only.

Carcinogenesis and Mutagenesis
See **TOXICOLOGY**.

Ophthalmologic
Cyclosporine ophthalmic emulsion, 0.05% w/v 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.

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

TEVA-CYCLOSPORINE 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 TEVA-CYCLOSPORINE.

Immune
There is the potential to experience hypersensitivity to TEVA-CYCLOSPORINE. Reactions of severe angioedema, face swelling, tongue swelling, pharyngeal edema, dyspnea and urticaria have been reported with the use of cyclosporine ophthalmic emulsion (see Post-Market Adverse Drug Reactions). If an allergic reaction occurs, patients should be advised to discontinue the drug.

Occupational Hazards
TEVA-CYCLOSPORINE 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.

Special Populations

Pregnant Women: There are no adequate data from the use of cyclosporine ophthalmic emulsion in pregnant women. Studies in animals have shown reproductive toxicity at high maternotoxic doses. See **TOXICOLOGY**.

TEVA-CYCLOSPORINE should not be used during pregnancy unless the benefits outweigh the risks.

Nursing Mothers: 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 cyclosporine, caution should be exercised when TEVA-CYCLOSPORINE is administered to a nursing woman.

Pediatric Use: The safety and efficacy of cyclosporine ophthalmic emulsion have only been studied in adults.

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

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most common adverse event following the use of cyclosporine ophthalmic emulsion, 0.05% w/v is ocular burning.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions 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 drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

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 was 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 1: 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)

Reported Term	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 (%)
Special Senses			
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%)	-
Body as a Whole			
Headache	7 (1.6%)	5 (1.1%)	2 (0.6%)

Note that active events are reported over 12 months; vehicle events are reported for six month exposure period.
NOS: Not Otherwise Specified

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

Less Common Clinical Trial Adverse Drug Reactions (<1%)

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.

Digestive System: dryness oral, nausea, salivary gland enlargement, stomatitis ulcer

Musculoskeletal System: arthralgia

Nervous System: dizziness

Respiratory System: rhinitis, infection sinus

Skin: rash, alopecia

Special Senses: conjunctivitis (NOS), oedema eyelid, blepharitis, erythema eyelid, asthenopia, chalazion, conjunctivitis bacterial, corneal abrasion, corneal infiltrates, corneal neovascularisation, eczema eyelid, oedema eye, conjunctival haemorrhage, keratitis herpes simplex, keratitis superficial punctate, lacrimation increased, pain ear, ulcer corneal (NOS), ulcerative keratitis, vitreous floaters

Post-Market Adverse Drug 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 swelling; hypersensitivity including severe angioedema, face swelling, tongue swelling, pharyngeal edema, dyspnea, urticaria; burning sensation; pruritus; superficial injury of the eye (from the vial touching the eye during administration).

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 cyclosporine ophthalmic emulsion, 0.05% w/v following ocular administration. Therefore, no interaction of topically applied TEVA-CYCLOSPORINE with systemic drugs is expected to occur.

Drug-Drug Interactions

Interactions with other drugs have not been established.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

There are no special dosing considerations which need to be taken into account prior to initiating therapy with TEVA-CYCLOSPORINE ophthalmic emulsion, 0.05% w/v.

Recommended Dose and Dosing Adjustment
The recommended dose is one drop of TEVA-CYCLOSPORINE, 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 cyclosporine ophthalmic emulsion (up to 40 months). It is expected that use of the product will continue long term.

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

The emulsion from one individual single-use ampoule 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 ampoule 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 ampoule container to the eye.

TEVA-CYCLOSPORINE 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 TEVA-CYCLOSPORINE.

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

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.

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 ampoule of 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 ampoule by a child weighing 14 kg (30 lb) would be approximately 140 times lower than the recommended starting dose of NEORAL®.

In case of suspected overdose, particularly accidental oral ingestion, contact your regional Poison Control Centre.

ACTION AND 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 *keratoconjuncitivitis sicca* (KCS), cyclosporine emulsion is thought to act as a partial immunomodulator. The exact mechanism of action is not known.

Pharmacodynamics

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

Pharmacokinetics

Blood cyclosporin A concentrations were measured using a specific high pressure liquid chromatography-mass spectrometry assay. Blood concentrations of cyclosporine A, in all the samples collected, after topical administration of cyclosporine ophthalmic emulsion 0.05% twice daily in humans for up to 12 months, were below the 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.

Special Populations and Conditions

Hepatic and 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 cyclosporine ophthalmic emulsion, 0.05% w/v, no increased risk in patients with impaired renal or hepatic function would be expected to occur following the use of TEVA-CYCLOSPORINE.

STORAGE AND STABILITY

TEVA-CYCLOSPORINE ophthalmic emulsion, 0.05% w/v should be stored at 15°-25°C. Patients should be instructed to keep unused ampoules in the foil envelope until use.

DOSAGE FORMS, COMPOSITION AND PACKAGING

TEVA-CYCLOSPORINE ophthalmic emulsion, 0.05% w/v is available as a sterile preservative-free emulsion supplied in low density polyethylene single use ampoules containing 0.4 mL each, packaged in trays containing 30 ampoules.

Each mL of emulsion contains cyclosporine 0.5 mg with the following non-medicinal ingredients: carbomer copolymer type A, castor oil, glycerin, polysorbate 80, purified water and sodium hydroxide to adjust the pH.

PART II : SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

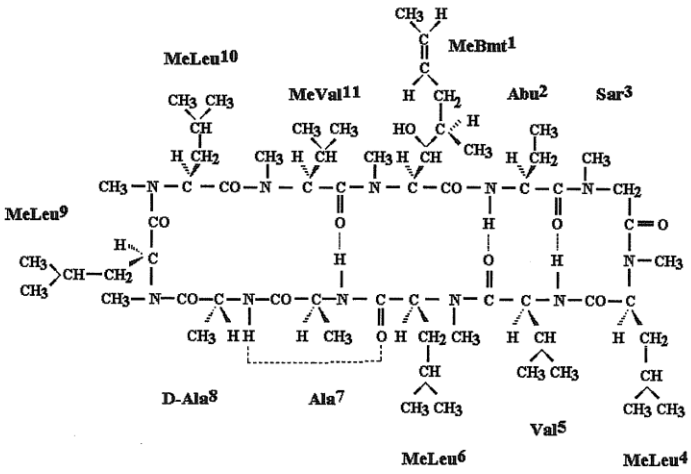
Proper name: Cyclosporine

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: $C_{62}H_{111}N_{11}O_{12}$

Molecular mass: 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 144-146°C.

CLINICAL TRIALS

Study Demographics and Trial Design

Details on the patient demographics for the three key vehicle-controlled studies conducted in patients with moderate to severe *keratoconjunctivitis sicca* are provided in Table 2. 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 *keratoconjunctivitis sicca* were included in the ITT population. Patient age ranged from 18.4 to 90.3 years, with a mean age (± SD) across studies of 58.6 ± 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).

Table 2: Summary of Patient Demographics for Clinical Trials in Patients with Moderate to Severe *keratoconjunctivitis sicca*

Study #	Trial Design	Dosage, Route of Administration and Duration[1]	Study Subjects in ITT Population	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

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).

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 4).

Table 3: 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

Table 4: 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).

DETAILED PHARMACOLOGY

Pharmacology

Topical use of cyclosporine exerts a local effect, only, 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.[6,11]

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).[6] 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.[7,14] It prevents the synthesis and/or secretion of several TH1 pro-inflammatory cytokines such as IL-2, IL-6, IFN-γ,[15,20] IL-8,[22] and TNF-α.[17] It is also known to upregulate secretion of TH2-type anti-inflammatory cytokines, including IL-13.[23] 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.

Preclinical Pharmacokinetics:

Ocular Metabolism

Ocular tissues in albino rabbits do not metabolize cyclosporine. After a single 50 µL eye drop of 0.2% 3H-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 eye drop 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 eye drop 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 twice-daily (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 choroidretina, melanin binding is unlikely in pigmented animals or humans.

Clinical Pharmacokinetics:

Blood concentrations of cyclosporin A following ophthalmic administration of cyclosporine ophthalmic emulsions were measured in human blood using a sensitive liquid chromatography/ mass spectrometry-mass spectrometry (LC/MS-MS) assay specific for cyclosporin A. The lower limit of quantitation was 0.1 ng/mL.

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 cyclosporin 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 eye drop 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 cyclosporin 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 5: Trough and Maximum Concentrations of cyclosporin 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 5. Cyclosporin A was not detectable in the blood of vehicle-treated patients or during pre-study qualification. Ophthalmic administration of cyclosporine emulsions up to 0.4% produced blood cyclosporin 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 cyclosporin A**.**

Blood cyclosporin 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 cyclosporin 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 cyclosporin 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 ≤0.144 ng/mL. Of the three patients whose cyclosporin 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 cyclosporin 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 cyclosporin 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 cyclosporin 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 cyclosporin 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 post-dose 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 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.

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. Details of the study conduct and results may be referred to in Tables 7 through 9.

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). No changes in the peripheral blood (white blood cells [WBC] and lymphocytes) were noted which suggests no impact on the systemic immune system.

In organ transplant patients receiving high doses of cyclosporine systemically, rare cases of visual disturbances due to morphological cerebral changes have been observed.[10,13,16] However, no neurotoxicity was observed following topical cyclosporine in these animal safety studies. All of the ocular tissues were unaffected.

Blood concentrations of cyclosporin 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.

Table 6: A Three Month Ocular and Systemic Toxicity Study with a One-Month Recovery Period in New Zealand White Rabbits

Species and Strain	Animals/ Group	Emulsions	Dose & Route	Dosing Duration	Parameters Measured	Results
New Zealand white rabbit	10 males and 10 females per group 8/sex/group sacrificed after 3 months 2/sex/group sacrificed after 1-month recovery	Vehicle of 0.4% cyclosporine, 3x/day at ~3 hr intervals 0.05% cyclosporine, 3x/day at ~3 hr intervals 0.2% cyclosporine, 3x/day at ~3 hr intervals 0.4% cyclosporine, 3x/day at ~3 hr intervals	~40 µL eye drop to 1 eye only	3 months followed by a 1-month recovery period	Clinical observations, gross ocular observations, ophthalmoscopic and slit lamp examinations, body weight, hematology, serum chemistry, blood drug concentration, organ weight, and macroscopic and microscopic examinations	Transient, slight ocular discomfort lasting, in most cases, no more than 30 seconds was observed in all animals, including the vehicle group animals. Transient, slight conjunctival hyperemia was observed with a dose-related incidence throughout the treatment period. There were no compound-related effects on clinical signs, slit lamp biomicroscopy, ophthalmoscopy, body weight, hematology, blood chemistry, organ weight, and macroscopic and microscopic examinations. Blood cyclosporin A concentrations in animals treated with 0.05% cyclosporine emulsion were generally below the quantitation limit of 0.2ng/mL in rabbit blood. In both sexes combined, mean C_{max} were 1.48 and 0.721 ng/mL after 3 months treatment with 0.2% and 0.4% cyclosporine emulsion, respectively. The highest individual blood C_{max} of 2.79 and 8.58 ng/mL were seen in one 0.4%-treated rabbit and one 0.2%-treated rabbit, respectively. Except for these 2 concentrations, the majority of individual blood concentrations in 0.2%- and 0.4%-treated animals were below 1.0 ng/mL. The mean $AUC_{0\text{-tlast}}$ values after dosing with 0.2% and 0.4% cyclosporine ophthalmic emulsions in rabbits were 4.52 and 4.28 ng·hr/mL, respectively.

Abbreviations: C_{max} = maximum concentration; $AUC_{0\text{-tlast}}$ = area under the curve of tissue concentration versus time, from the time of dose instillation through the last sampling time or the last sampling time at which cyclosporin A was quantifiable (tlast).

Table 7: Six Month Ocular and Systemic Toxicity Study with a 2-Month Recovery Period in New Zealand White Rabbits

Species and Strain	Animals/ Group	Emulsions	Dose & Route	Dosing Duration	Parameters Measured	Results
New Zealand white rabbit	15 males and 15 females per group 10/sex/group sacrificed after 6 months 5/sex/group sacrificed after 2-month recovery Additional 3/sex satellite animals assigned to 0.4% dose group (6x/day), used for blood drug concentration on day 8	Vehicle of 0.2% cyclosporine, 3x/day at ~3 hr intervals Vehicle of 0.4% cyclosporine, 6x/day at ~2 hr intervals 0.05% cyclosporine, 3x/day at ~3 hr intervals 0.2% cyclosporine, 3x/day at ~3 hr intervals 0.4% cyclosporine, 3x/day at ~3 hr intervals 0.4% cyclosporine, 6x/day at ~2 hr intervals	~40 µL eye drop to 1 eye only	6 months followed by a 2-month recovery period	Clinical observations, gross ocular observations, ophthalmoscopic and slit lamp examinations, body weight, hematology, serum chemistry, blood drug concentration, organ weight, and macroscopic and microscopic examinations	Transient, slight ocular discomfort lasting, in most cases, no more than 30 seconds was observed in all animals, including the vehicle group animals. Transient, slight conjunctival hyperemia was observed with higher incidence in cyclosporine-treated animals when compared to controls. During th[e] 1st week of the study, sporadic instances of slight to mild iritis and slight aqueous flare were observed in cyclosporine-treated animals, however these findings did not last more than 2 days and were not dose-related. There were no gross ocular findings during the recovery period. The grossly observed hyperemia was confirmed at the slit lamp examinations at 1 month, 3 months, and at the end of the treatment period in which slight to moderate conjunctival congestion and slight discharge were observed in all treatment groups except the 0.2% vehicle control. There were no compound-related effects on clinical signs, ophthalmoscopy, body weight, hematology, blood chemistry, organ weight, and macroscopic and microscopic examinations. Blood cyclosporin A concentrations were low, and increased less than proportionally to dose. In both sexes combined, mean C_{max} in 0.05%, 0.2%, and 0.4% 3 times daily, and 0.4% 6 times daily cyclosporine emulsion groups after 6 months treatment were 0.328, 0.997, 0.570, and 1.36 ng/mL, respectively. The highest individual peak blood cyclosporin A concentration of 3.75 ng/mL was seen in one rabbit dosed with 0.2% cyclosporine emulsion. The majority of the individual blood C_{max} values were below 1.0 ng/mL. The mean $AUC_{0\text{-}tlast}$ ($6.5 \leq t_{last} \leq 24$ hr) at these doses were 3.48, 9.25, 6.85, and 16.7 ng·hr/mL, respectively.

Abbreviations: C_{max} = maximum concentration; $AUC_{0\text{-}tlast}$ = area under the curve of tissue concentration versus time, from the time of dose instillation through the last sampling time or the last sampling time at which cyclosporin A was quantifiable (tlast).

Table 8: 52-Week Ocular and Systemic Study of Cyclosporine in Dogs with an 8-Week Recovery Period

Species and Strain	Animals/ Group	Emulsions	Dose & Route	Dosing Duration	Parameters Measured	Results
Dog, beagle	6 males and 6 females per group 4/sex/group sacrificed after 52 weeks 2/sex/group sacrificed after 8-week recovery	Vehicle of 0.4% cyclosporine, 6x/day at ~2 hr intervals 0.1% cyclosporine, 3x/day at ~3 hr intervals 0.2% cyclosporine, 3x/day at ~3 hr intervals 0.4% cyclosporine, 6x/day at ~2 hr intervals	~40 µL eye drop to 1 eye only	52 weeks followed by a 8-week recovery period	Clinical observations, gross ocular observations, ophthalmoscopic and slit lamp examinations, body weight, food consumption, hematology, blood chemistry, urine analysis, blood pressure electro-cardiography, blood drug concentration, organ weight, and macroscopic and microscopic examinations	No evidence of discomfort was associated with application of the eye drops in any of the dogs. Reddened conjunctiva was noted sporadically in individual animals within both the vehicle control and cyclosporine-treated animals, but there was no suggestion of a dose response. There was a tendency toward an increased tears of the treated eye observed in the 0.4% cyclosporine-treated animals. No changes were observed upon ophthalmoscopic and slit lamp examinations. There were no compound-related effects on clinical signs, body weight, food consumption, hematology, blood chemistry, urine analysis, blood pressure, electrocardiography, organ weight, and macroscopic and microscopic examinations. The maximum blood cyclosporin A concentration following instillation of 0.1% 3 times daily, 0.2% 3 times daily, and 0.4% 6 times daily was below 1.2 ng/mL. Mean blood C_{max} following instillation of 0.1% 3 times daily, 0.2% 3 times daily, and 0.4% cyclosporine emulsion 6 times daily for 49 weeks were 0.299, 0.459, and 0.675 ng/mL, respectively. The mean $AUC_{0\text{-tlast}}$ ($9 \leq t_{last} \leq 24$ hr) after 0.1% 3 times daily, 0.2% 3 times daily, and 0.4% cyclosporine emulsion 6 times daily were 2.35, 3.39, and 9.55 ng·hr/mL, respectively. The mean C_{max} and $AUC_{0\text{-tlast}}$ indicated that blood concentrations were dose-dependent. Comparisons of minimum concentrations (C_{min}), C_{max} and $AUC_{0\text{-tlast}}$ during weeks 1 and 49 for each treatment group indicated no marked systemic drug accumulation.

Abbreviations: C_{max} = maximum concentration; $AUC_{0\text{-tlast}}$ = area under the curve of tissue concentration versus time, from the time of dose instillation through the last sampling time or the last sampling time at which cyclosporin A was quantifiable (tlast).

Carcinogenesis and Mutagenesis:
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.

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).

Reproductive 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).

REFERENCES

1. Anonymous. 2007 Report of the International Dry Eye WorkShop (DEWS). The Ocular Surface, April 2007; 5(2):65-204.

2. Barber LD, Pflugfelder SC, Tauber J, Foulks GN. Phase III safety evaluation of cyclosporine 0.1% ophthalmic emulsion administered twice daily to dry eye disease patients for up to 3 years. Ophthalmology 2005;112(10):1790-1794.

3. Baudouin C, Brignole F, Pisella P, De Saint Jean M, Goguel A. Flow cytometric analysis of the inflammatory marker HLA DR in dry eye syndrome: Results from 12 months of randomized treatment with topical cyclosporin A. In: Sullivan David A, ed. Advances in Experimental Medicine and Biology. Volume 506. Lacrimal Gland, Tear Film, and Dry eye Syndrome Basic Science and Clinical Relevance. Part B ed. 233 Spring Street, New York, New York 10013: Kluwer Academic/Plenum Publishers, New York 2002;506:761-769.

4. Behrens A, Doyle JJ, Stern L, et al. Dysfunctional Tear Syndrome: a Delphi approach to treatment recommendations. Cornea 2006;25(8):900-907.

5. Belin MW, Bouchard CS, Phillips TM. Update on topical cyclosporin A: background, immunology, and pharmacology. Cornea 1990; 9:184-195.

6. Borel JF, Baumann G, Chapman I, Donatsch P, et al. *In Vivo* pharmacological effects of ciclosporin and some analogues. Adv Pharmacol 1996:115-246.

7. Boss V, Wang X, Koppelman LF, et al. Histamine induces nuclear factor of activated T cell-mediated transcription and cyclosporin A-sensitive interleukin-8 mRNA expression in human umbilical vein endothelial cells. Mol Pharmacol 1998; 54:264-72.

8. Donnenfeld E, Pflugfelder SC Topical ophthalmic cyclosporine: Pharmacology and clinical uses. Surv Ophthalmol 2009;54(3):321-338.

9. Gao J, Schwalb TA, Addeo JV, et al. The role of apoptosis in the pathogenesis of canine Keratoconjunctivitis Sicca: The effect of topical cyclosporin A therapy. Cornea 1998;17(6):654-63

10. Ghalie R, Fitzsimmons WE, Bennett D, et al. Cortical blindness: a rare complication of cyclosporine therapy. Bone Marrow Transplant 1990;6:147-149.

11. Kahan BD. Drug Therapy. Cyclosporine. New Eng J Med 1989;321:1725-38.

12. Kunert KS Tisdale AS, Gipson IK. Goblet cell numbers and epithelial proliferation in the conjunctiva of patients with dry eye syndrome treated with cyclosporine. Arch Ophthalmol 2002;120(3):330-337.

13. Memon M, deMagalhaes-Silverman M, Bloom EG, et al. Reversible cyclosporine-induced cortical blindness in allogenic bone marrow transplant recipients. Bone Marrow Transplant 1995;15:283-286.

14. Meyer S, Kohler G, Joly A, et al. Cyclosporine A is an uncompetitive inhibitor of proteasome activity and prevents NF-κB activation. FEBS Letters 1997;41(3):354-8.

15. Mitruka SN, Pham SM, Zeevi A, Li S, Cai J, Burckart GJ, Yousem SA, Keenan RJ, Griffith BP. Aerosol ciclosporin prevents acute allograft rejection in experimental lung transplantation. J Thorac Cardiovasc Surg 1998;115(1):28-36.

16. Nussbaum ES, Maxwell RE, Bitterman PB, et al. Cyclosporine A toxicity presenting with acute cerebellar edema and brainstem compression. J Neurosurg 1995;82:1068-1070.

17. Pette M, Pette DF, Muraro PA, Martin R, McFarland HF. *In vitro* modulation of human, auto reactive MBP-specific CD4+ T-cell clones by ciclosporin A. J Neuroimmunol 1997;76(1-2):91-9.

18. Pflugfelder SC, Solomon A, Stern ME. The diagnosis and management of dry eye; A twenty-five-year review. Cornea 2000; 19(5):644-649.

19. Product Monograph, NEORAL® / SANDIMMUNE® 2008.

20. Schliephake H, Redecker K, Schmelzeisen R, Maschek H. Cytokines and cytokine receptors in mouth mucosa of immune suppressed patients. Mund Kiefer Gesichtschir 1997;192:111-4 (article in German, abstract in English).

21. Stern ME, Beuerman RW, Fox RI, et al. The pathology of dry eye: The interaction between the ocular surface and the lacrimal glands. Cornea 1998;17(6):584-9.

22. Svecova D, Kawashima T, Ohkawara A. Production of IL-8 by the THP-1 monocyte cell line is regulated differently by ciclosporin and retinoic acid. Bratisl Lek Listy 1998;99(1)48-53 (article in Slovac, abstract in English).

23. Van der Pouw Kraan TC, Boeije LC, Troon JT, Rutschmann SK, Wijdenes J, Aarden LA. Human IL-13 production is negatively influenced by CD3 engagement. Enhancement of IL-13 production by ciclosporin A. J Immunol 1996;156(5):1818-23.

24. Restasis® Product Monograph, Allergan Inc. Submission Control No. 157208, Date of Revision: October 3, 2012

PART III: CONSUMER INFORMATION

PrTEVA-CYCLOSPORINE
Cyclosporine
Ophthalmic Emulsion, 0.05% w/v
Teva Standard

This leaflet is Part III of a three-part "Product Monograph", published when TEVA-CYCLOSPORINE was approved for sale in Canada, and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about TEVA-CYCLOSPORINE. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
TEVA-CYCLOSPORINE is used to treat certain patients whose eyes are not producing enough tears to keep the eye moist and comfortable.

What it does:
TEVA-CYCLOSPORINE acts as a topical immunomodulator with anti-inflammatory effects.

When it should not be used:
TEVA-CYCLOSPORINE should not be used if
- you have an eye infection
- you are hypersensitive to cyclosporine or any of the other ingredients in the formulation (see **What the non-medicinal ingredients are**).

What the medicinal ingredient is:
The active ingredient is cyclosporine.

What the non-medicinal ingredients are:
The other ingredients in the formulation are carbomer copolymer type A, castor oil, glycerin, polysorbate 80, purified water and sodium hydroxide (to adjust pH).

What dosage forms it comes in:
TEVA-CYCLOSPORINE is available as a sterile ophthalmic emulsion, in a 0.4 mL single use plastic ampoule.

WARNINGS AND PRECAUTIONS

BEFORE you use TEVA-CYCLOSPORINE, talk to your doctor or pharmacist if:

You have a history of *herpes keratitis.* Cyclosporine ophthalmic emulsion has not been tested for use in people with this condition

Your dry eyes are the result of Vitamin A deficiency or scarring. Cyclosporine ophthalmic emulsion has not been studied in people with these causes of dry eyes.
You drive or operate machinery. TEVA-CYCLOSPORINE 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.

You are breast feeding a baby. It is not known whether or not cyclosporine is passed into breast milk.

You are pregnant or planning to become pregnant. While there are no known adverse effects on human pregnancy, there is very little information available, and you should decide with your doctor how best to proceed.

Do not administer TEVA-CYCLOSPORINE while you wear contact lenses. If you must wear contact lenses, remove the lenses before applying TEVA-CYCLOSPORINE. Wait for 15 minutes before you put your contact lenses back in.

You should also avoid touching the tip of the ampoule to the eye or any surface as this may contaminate the emulsion, or touching the eye may cause injury.

INTERACTIONS WITH THIS MEDICATION

No drug interaction studies have been performed with cyclosporine ophthalmic emulsion . Concomitant use with other eye products should be discussed with your doctor beforehand.

PROPER USE OF THIS MEDICATION

Usual Adult Dose:
The usual adult dose of TEVA-CYCLOSPORINE is one drop into each affected eye. This dose should be applied twice a day – about 12 hours apart.

Before using, gently shake the ampoule by tipping it up and down a few times until the emulsion is white and appears the same throughout the ampoule.

Each individual, single-use ampoule should be used immediately after opening for administration to one or both eyes, and the remaining contents discarded immediately after administration.

TEVA-CYCLOSPORINE may be used together with artificial tears. Wait 15 minutes between using TEVA-CYCLOSPORINE and the artificial tear product.

Overdose:

If you have taken too much TEVA-CYCLOSPORINE,

particularly accidental oral ingestion, contact your healthcare practitioner (e.g. doctor), hospital emergency department or regional Poison Control Centre, 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.

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

Ocular burning is a very common (≥1/10) adverse event with TEVA-CYCLOSPORINE. Other common events (≥1/100) are eye irritation, headache, foreign body sensation in eye, ocular / conjunctival hyperaemia (redness), eye pain, eye stinging, eye discharge, photophobia, eye pruritus, blurred vision, dry eye. These events usually get better on their own, as your eye becomes used to treatment with TEVA-CYCLOSPORINE.

There is the potential to experience an allergic reaction to TEVA-CYCLOSPORINE. Reactions of face swelling, tongue swelling, throat swelling, shortness of breath and itchy skin rash have been reported with the use of cyclosporine ophthalmic emulsion. If an allergic reaction occurs, discontinue the drug and contact your physician.

This is not a complete list of side effects. For any unexpected effects while taking TEVA-CYCLOSPORINE, contact your doctor or pharmacist.

HOW TO STORE IT

TEVA-CYCLOSPORINE should be stored at 15-25ºC. Keep unused ampoules in foil envelope until use.

Keep out of reach and sight of children.

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 (http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php) 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.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be found by contacting Teva Canada Limited by:
Phone: 1-800-268-4127 ext. 3;
Email: druginfo@tevacanada.com; or
Fax: 1-416-335-4472

This leaflet was prepared by:

Teva Canada Limited
30 Novopharm Court
Toronto, Ontario
Canada, M1B 2K9

www.tevacanada.com

Date prepared: March 14, 2017