PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]Restasis MultiDose™

Cyclosporine Ophthalmic Emulsion

Emulsion, 0.05% w/v, ophthalmic

Manufacturer's standard

Anti-Inflammatory / Immunomodulator

AbbVie Corporation
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RECENT MAJOR LABEL CHANGES

No recent changes; new product monograph.

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

Restasis MultiDose™ (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 Restasis MultiDose™ alone has not been demonstrated in patients with more severe disease (Level 4 DEWS Classification).[1]

1.1 Pediatrics

Pediatrics (<18 years 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 MultiDose™ is contraindicated in:

- 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.

- Patients with active ocular infections

3 DOSAGE AND ADMINISTRATION

3.1 Dosing Considerations

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

3.2 Recommended Dose and Dosage Adjustment

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

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

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 MultiDose™ (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.

3.3 Administration

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

Patients should be advised to avoid touching the tip of the bottle 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 bottle container to the eye.

Restasis MultiDose™ 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 MULTIDOSE™.

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

See PATIENT MEDICATION INFORMATION, including instructions on the preparation of the bottle for first-time use. By design, there may be residual volume of Restasis MultiDose™ in the bottle at the end when used as directed. Patients should be instructed not to dispense this residual volume.

3.4 Missed Dose

If a dose of Restasis MultiDose™ 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.

4 OVERDOSAGE

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 multi dose bottle of 0.05% cyclosporine emulsion contains 2.75 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 multi dose bottle by a child weighing 14 kg (30 lb) would be approximately 10 times lower than the recommended starting dose of NEORAL®.

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

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table – Dosage Forms, Strengths, Composition and Packaging.

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

Restasis MultiDose™ is available as a sterile preservative-free emulsion supplied in low density polyethylene multidose bottle containing 5.5 mL. By design, there may be residual volume of Restasis MultiDose™ in the bottle at the end when used as directed.

6 WARNINGS AND PRECAUTIONS

General
For ophthalmic use, only.

Immune
There is the potential to experience hypersensitivity to Restasis MultiDose™. Reactions of severe angioedema, face swelling, tongue swelling, pharyngeal edema, dyspnea and urticaria have been reported with the use of Restasis MultiDose™ (See Post-market Adverse Drug Reactions). If an allergic reaction occurs, patients should be advised to discontinue the drug.

Ophthalmologic
Restasis MultiDose™ 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 bottle 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 bottle container to the eye.

Restasis MultiDose™ 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 MultiDose™.

Driving and Operating Machinery
Restasis MultiDose™ 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.

Carcinogenesis and Mutagenesis
See NON-CLINICAL TOXICOLOGY.

6.1 Special Populations

6.1.1 Pregnant Women

There are no adequate data from the use of Restasis MultiDose™ in pregnant women. Restasis MultiDose™ should be used with caution during pregnancy. Cyclosporine ophthalmic emulsion 0.05% is not detected systemically following clinical topical ocular administration (lower quantitation limit of 0.1 ng/mL), and maternal use is not expected to result in fetal exposure to the drug (See 9.3 Pharmacokinetics). Studies in animals have shown reproductive toxicity only at high maternotoxic doses. See NON-CLINICAL TOXICOLOGY.

6.1.2 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 MultiDose™, caution should be exercised when Restasis MultiDose™ is administered to a nursing woman.

6.1.3 Pediatrics

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

6.1.4 Geriatrics

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

7 ADVERSE REACTIONS

7.1 Adverse Reaction Overview

The most common adverse event following the use of Restasis MultiDose™ is ocular burning.

7.2 Clinical Trial Adverse 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 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 6 month exposure period.
NOS – not otherwise specified

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

7.3 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.

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.

7.4 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 swelling; hypersensitivity including severe angioedema, face swelling, tongue swelling, pharyngeal edema, dyspnea, urticaria; burning sensation; pruritus; superficial injury of the eye (from the bottle tip touching the eye during administration).

8 DRUG INTERACTIONS

8.1 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 MultiDose™ following ocular administration. Therefore, no interaction of topically applied Restasis MultiDose™ with systemic drugs is expected to occur.

8.2 Drug-Drug Interactions

Interactions with other drugs have not been established.

8.3 Drug-Food Interactions

Interactions with food have not been established.

8.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

8.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

Cyclosporine is an immunosuppressive agent, however, as it is topically applied, systemic immunosuppression is not likely to occur.

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.

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).

Topical cyclosporine emulsion is thought to exert its therapeutic ophthalmic effect in part by its local immunomodulating activity rather than any systemic immunosuppressant effect.

9.2 Pharmacodynamics

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

9.3 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.

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 MultiDose™, no increased risk in patients with impaired hepatic function would be expected to occur following the use of Restasis MultiDose™.

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

10 STORAGE, STABILITY AND DISPOSAL

Restasis MultiDose™ should be stored at 15 – 25° C. Unused emulsion should be discarded 30 days after opening.

11 SPECIAL HANDLING INSTRUCTIONS

Patients should be advised to avoid touching the tip of the bottle 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 bottle container to the eye.

PART II: SCIENTIFIC INFORMATION

12 PHARMACEUTICAL INFORMATION

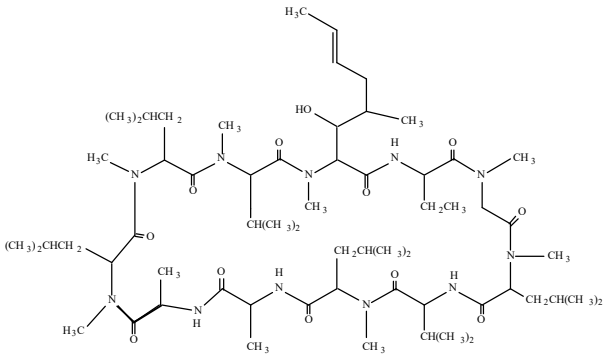
Drug Substance

Proper name: Cyclosporine

Chemical name: Cyclo[[(E)-(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoyl]-L-2-aminobutyryl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl]

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

Structural formula:



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

13 CLINICAL TRIALS

13.1 Trial Design and Study Demographics

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 on the following page. 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).

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*

13.2 Study Results

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 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]

Study #	Endpoint	Proportion of Patients with a Score of 0 (N)		P value Relative Risk [95% CI]
		Cyclosporine 0.05%	Vehicle	
	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).

14 NON-CLINICAL 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 eyedrop 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 concentrat	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 eyedrop 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 the 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

Species and strain	Animals/ group	Emulsions	Dose & route	Dosing duration	Parameters measured	Results
	ion on day 8					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 eyedrop to 1 eye only.	52 weeks followed by an 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.

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 eyedrop to 1 eye only.	52 weeks followed by an 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).

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

[Pr]Restasis MultiDose™
Cyclosporine Ophthalmic Emulsion

Read this carefully before you start taking Restasis MultiDose™ 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 MultiDose™.

What is Restasis MultiDose™ used for?

- It 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 MultiDose™ is right for you.

How does Restasis MultiDose™ work?

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

What are the ingredients in Restasis MultiDose™?

Medicinal ingredients: cyclosporine.
Non-medicinal ingredients: Carbomer Copolymer Type A, castor oil, glycerin, polysorbate 80, purified water and sodium hydroxide.

Restasis MultiDose™ comes in the following dosage forms: Emulsion, 0.05% w/w.

Do not use Restasis MultiDose™ if:

- You have an eye infection.
- You are hypersensitive to cyclosporine or any of the other ingredients in Restasis MultiDose™.
- You are allergic to any component of the Restasis MultiDose™ container.

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

- You have or have had *herpes keratitis.* Restasis MultiDose™ 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.

- Your dry eyes are the result of Vitamin A deficiency or scarring. Restasis MultiDose™ has not been studied in people with these causes of dry eyes.

- You drive or operate machinery. Restasis MultiDose™ may cause your vision to blur right after you put the drops in. Wait until your vision clears before you drive or operate a machine.

- You are breastfeeding a baby. It is not known if Restasis MultiDose™ passes into breast milk.

- You are pregnant or planning to become pregnant.

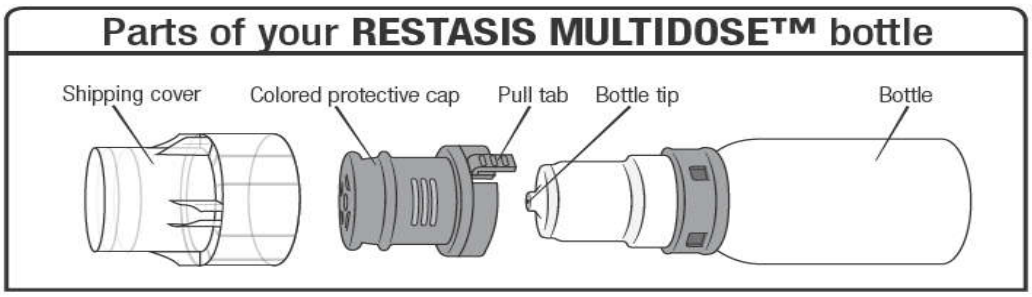
Other warnings you should know about:
Do not administer Restasis MultiDose™ while you wear contact lenses. If you must wear contact lenses, remove the lenses before applying Restasis MultiDose™. Wait for 15 minutes before you put your contact lenses back in.

You should avoid touching the tip of the bottle to the eye or any surface. This may contaminate the emulsion, and touching the eye may cause injury.

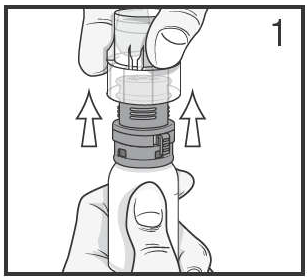
Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take Restasis MultiDose™:
Before using, gently shake the bottle by turning it upside down a few times to make sure the emulsion is mixed well.

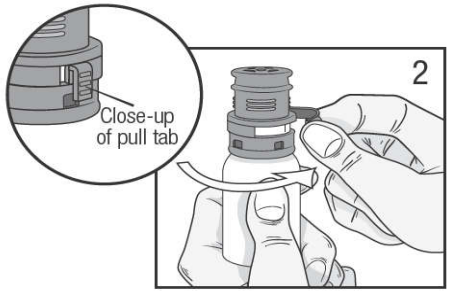
Restasis MultiDose™ may be used together with artificial tears. Wait 15 minutes between using Restasis MultiDose™ and the artificial tear product.



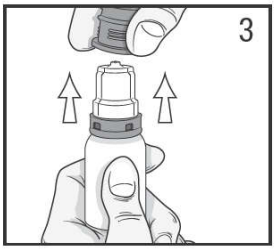
Preparation for First-Time Use
Step 1: Pull off shipping cover by pulling straight up. Throw the shipping cover away. Do not use Restasis MultiDose™ if shipping cover or pull tabs are damaged or missing.



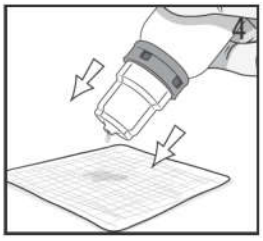
Step 2: Remove the pull tab on the olive green colored protective cap by pulling the end of the pull tab away from the bottle then winding it counterclockwise. Throw away the pull tab.



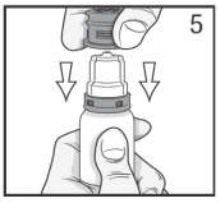
Step 3: Remove the olive green colored protective cap by pulling it straight up. Keep the colored protective cap.



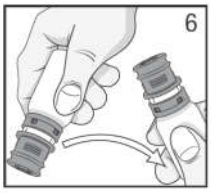
Step 4: Prime the bottle for first time use by holding the bottle with the tip pointing down. Slowly squeeze the bottle to deliver one drop onto a tissue to get used to the pressure and time required to deliver one drop. Do this twice. Do not let the bottle tip touch the tissue.



Step 5: The bottle is now ready for use. After use, recap the bottle with the olive green colored protective cap by pushing straight down onto the bottle.



Preparation for Use:
Step 6: Turn the bottle upside down a few times before giving your dose to make sure the medicine is mixed well.



Step 7: Hold the bottle with the tip pointing down and squeeze the bottle gently in the middle to let one drop fall into the eye you are treating. Please note that there might be a few seconds delay between squeezing and the drop coming out. Do not squeeze the bottle too hard to avoid releasing too many drops. Once administered, replace the olive green colored protective cap.

By design, there may be a small quantity of Restasis MultiDose™ remaining in the bottle at the end when used as directed. Do not try to use the remaining quantity in the bottle.

Usual dose:
The usual adult dose of Restasis MultiDose™ is one drop into each eye you are treating. This dose should be applied twice a day – about 12 hours apart.

Overdose:

If you think you have taken too much Restasis MultiDose™, contact your 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 take a double dose to make up for a missed dose.

What are possible side effects from using Restasis MultiDose™?

These are not all the possible side effects you may feel when taking Restasis MultiDose™. If you experience any side effects not listed here, contact your healthcare professional.

Side effects may include:

Eye Disorders
- burning sensation in the eye
- blurred vision
- dry eye
- eye discharge
- eye irritation
- eye itching
- eye pain

- eye redness
- 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.			X

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

Storage:
Restasis MultiDose™ should be stored at 15-25°C. Discard unused emulsion 30 days after opening.

Keep out of reach and sight of children.

If you want more information about Restasis MultiDose™:
- 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 (http://hc-sc.gc.ca/index-eng.php); the manufacturer's website www.abbvie.ca, or by calling 1-888-704-8271.

This leaflet was prepared by AbbVie Corporation.

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