CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-023

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology/Biopharmaceutics Review

NDA: 21-023 SUBMISSION DATE: 2/25/99, 3/30/99

PRODUCT: Restatis™ 0.05%
(Cyclosporin Ophthalmic Emulsion)

SPONSOR: Allergan, Inc.
Irvine, CA.

REVIEWER: Veneeta Tandon, Ph.D.

Review of a NDA

I. Background

Cyclosporine ophthalmic emulsion 0.05% is indicated for [redacted]. It acts as an immunomodulator and an anti-inflammatory agent. Cyclosporin helps in suppressing the immune-based inflammation of the ocular surface, allowing for the secretion of more normal ocular surface supportive tears and a more stable tear film. Topical use of cyclosporin exerts a local effect only, an action termed immunomodulatory, rather than systemic immonosuppresive effect. Although cyclosporin is not a classical anti-inflammatory agent and has not been demonstrated to inhibit cyclo-oxygenase, it does inhibit inflammation in other ways. Cyclosporine prevents the synthesis and/or secretion of several TH1 pro-inflammatory cytokines, and is also known to upregulate secretion of TH2-type anti-inflammatory cytokines. Additionally, cyclosporine has been shown to regulate immune-based inflammation within ocular surface tissues by inhibiting intercellular adhesion molecule-1 (ICAM-1).

Current treatment options for dry eye are palliative, and provide symptomatic relief only without addressing the underlying mechanisms of the disease. Cyclosporine, as an immunomodulating agent, has been shown to break the cycle of the immune reactivity underlying the disease both in dry-eye dogs[1,2] and in dry-eye patients[3]. Cyclosporine reduces lacrimal gland lymphocytic infiltrates and improves tear production in KCS dogs [1,4,5] and in KCS patients with or without Sjögren's syndrome [2,3,6,7]. Power et al demonstrated that patients with secondary Sjögren's disease are undergoing continued

[1] Kaswan et al, Arch ophthalmol, 107:1210-1216, 1989
[2] Stern at al, Cornea, 17:584-589,1998
[3] Power et al, Cornea,12:507-511,1993
[4] Kaswan et al, Vet Clin North Am Small Anim prac, 20:583-613,1990
[5] Morgan et al, J Am Vet Assoc, 199:1043-1046, 1991
[6] Drosos el al, Ann Rheum Dis, 45:732-735,1986
[7] Laibovitz et al, Cornea, 12:315-323,1993

immune reactivity, indicated by the presence of significantly more CD4 (T-helper) cells than age/sex-matched controls. Following treatment with topical cyclosporine, there was a significant reduction in the number of CD4 cells in both the conjunctival epithelium and substantia propria, indicating immunopathological improvement.

Oral cyclosporin is available for the treatment of rheumatoid arthritis, psoriasis (2.5 to 5 mg/kg/day-NEORAL®) and systemic prophylaxis of organ transplant rejection (7-9 mg/kg/day-NEORAL®). SANDIMMUNE® is also used at higher doses, but has lower bioavailability as compared to NEORAL®. In contrast topical cyclosporin emulsion is to be used at the dose of 1 to 2 µg/kg/day.

Dosage and Administration

The recommended dosage is one drop (——) of RESTASIS™ (0.05%) instilled twice a day in each eye approximately 12 hours apart.

Foreign marketing history

Not yet marketed in any other country.

II. Recommendation

The cyclosporin concentrations were below the limit of quantitation in most samples. Only 9 samples out of 348 samples from the phase 2 and 3 studies had quantifiable concentrations, with a highest value of —— ng/ml. All these samples were from patients receiving 0.1% cyclosporin emulsion. The C_{max}, C_{min} and AUC_{0-12} were several orders of magnitude below than those produced by systemic treatments already approved for non-life threatening conditions. All patients treated with 0.05% cyclosporin emulsion, were below the detection limit of 0.1 ng/ml with up to 9 months of dosing.

The concentration-time profile of cyclosporin in tears over the course of one 12 hour dosing interval and the 12 month data from study 192371-002 has not been submitted yet. The application is approvable from the biopharmaceutics standpoint, contingent upon the availability of the remaining data and its appropriateness.

CONTENTS

III. Formulation

Ingredient	Concentration for 0.05% (%w/w) To-be marketed	Concentration for 0.1%% (%w/w) Not-to-be marketed
Cyclosporin USP	0.05	0.1
Castor oil PhEur		
Glycerine USP		
Polysorbate 80 NF		
Carbomer 1324 nF		
Sodium hydroxide NF		
Purified water USP		

IV. Analytical Validation

Cyclosporin A in human blood was analyzed using [redacted] and

LOQ: 0.1 ng/ml

Linearity: The linearity was tested over the concentration range [redacted] with a coefficient of correlation of [redacted] for day [redacted] of the validation, respectively.

Intra-day Precision and Accuracy: The accuracy of intra-day variability ranged from [redacted] of the nominal concentrations and precision (%CV) ranged from [redacted]

Inter-day Precision and Accuracy: The accuracy ranged from [redacted] of the nominal with a precision between [redacted]

Freeze-Thaw Stability: The mean percent differences from nominal were [redacted] at [redacted] respectively after [redacted]. The precision was [redacted] and [redacted] at [redacted] respectively.

Stability: At room temperature- Mean percentage difference from nominal was [redacted] after 24 hours and [redacted] after 48 hours for [redacted]. It was [redacted] after 24 hours and [redacted] after 48 hours for [redacted] Precision ranged from [redacted]

After [redacted] - mean percent difference was [redacted] and [redacted] for [redacted] and [redacted] respectively. The precision was [redacted], respectively.

In human blood, unextracted for 24 hours at room temperature- Mean percent difference from nominal was [redacted] and precision was [redacted], respectively.

Recovery: The percent recovery of the overall process which includes [redacted] and [redacted] was [redacted] which is unusually high.

V. Pharmacokinetic Studies

The human pharmacokinetics of cyclosporin ophthalmic emulsion has been evaluated in a phase II dose ranging study and a phase III safety and efficacy study for up to one year duration. Blood samples up to 9 months have been evaluated. The 12th month blood cyclosporin concentrations and concentration-time profile in tears up to 12 hours of dosing will be submitted later.

Quantitation of cyclosporin A was preferred in whole blood over plasma due to high blood-plasma concentrations ratios at very low doses of cyclosporin and even on systemic dosing. Cyclosporin has high affinity of blood cells than for plasma proteins. Preliminary in vitro experiments evaluating the blood-to-plasma concentration ratio suggested that blood concentrations of cyclosporin may be twice those of plasma.

Study # 192371-001 (PK-96-018)

A dose ranging study evaluating the safety, tolerability and efficacy of cyclosprorin (0.05, 0.1, 0.2, 0.4%) and vehicle ophthalmic emulsions in the treatment of moderate to severe keratoconjuctivitis sicca.

This study was a randomized, double-masked, parallel-group design in 162 subjects (26M and 136F) treated topically with either vehicle, 0.05%, 0.1%, 0.2% or 0.4% cyclosporin emulsion twice daily in each eye for 12 weeks.

Blood samples were collected from each subject at baseline, trough samples prior to morning dose following 1, 4, and 12 weeks of dosing. To obtain maximum blood concentrations for each treatment groups, blood samples were also collected at one of the study sites from approximately 3-5 subjects per treatment group at 1, 2 and 4 hours after the final dose at the end of 4 weeks of dosing. Peak blood concentrations are reported to occur between 1 and 4 hours after oral dosing. Blood samples were also collected at 4 weeks post treatment (week 16).

Results

Cyclosporin A was neither quantifiable in blood samples collected prestudy from all subjects nor in blood samples from vehicle-treated subjects after 1, 4 and 12 weeks of dosing. Trough samples after 1, 4 and 12 weeks of dosing with 0.05, 0.1, 0.2, and 0.4% cyclosporin twice daily were very low (less than 0.2 ng/ml). Only 5 out of 120 subjects (includes all dosing groups) showed detectable trough concentrations with values of _____ ng/ml. The ranges of trough blood concentrations for the four treatment groups after 1, 4 and 12 week of dosing and maximum blood concentration at 1, 2 and 4 hours after the last dose on week 12 are shown in the following table.

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