CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-023

PHARMACOLOGY REVIEW(S)

NDA21-023

Review and Evaluation of Pharmacology/Toxicology data

Key Words: Topical Cyclosporine eye drop, Dry eye, Apoptosis, Acinar Epithelium, Lacrimal gland

Reviewer: Asoke Mukherjee

Division of Anti-inflammatory, Analgesic and Ophthalmic Drug Products

HFD-550

Review Completion Date: June 2, 1999

Review Number: One

NDA: 21-023

Serial Number, Date and Type of Submission: Serial # 1, Original NDA Application under 505 (b)1, Feb 24, 1999

Information to the sponsor: Yes ( ) No (X)

Sponsor: Allergan Inc. California 92623

Manufacturer of Drug Substance:

Drug: Cyclosporine ophthalmic emulsion

Code Name: AGN 192371

Generic Name: Cyclosporine Ophthalmic Emulsion, 0.05% preservative free.

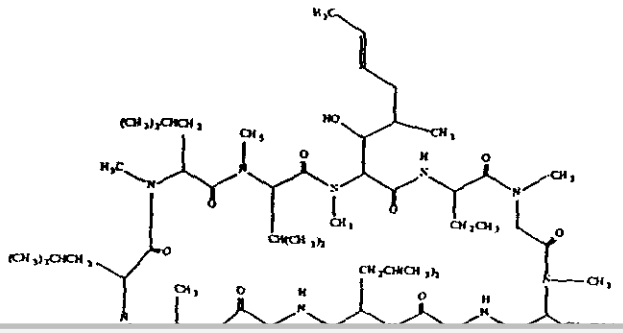
Trade Name: RESTASIS (proposed)

Chemical Name: Cyclo[[(E)-(2S,3R,4R)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoyl]-L-2aminobutyryl-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]

CAS Registry Number: 059865-13-3

Molecular Formula: $C_{62}H_{111}N_{11}O_{12}$. Molecular Weight: 1202.6

Structure:



Relevant NDA: [redacted] 50-733, [redacted], 50-574 and 50-573

Relevant IND: 32,133 and [redacted]

Relevant DMF: DMF [redacted] Type 1, DMF [redacted] type III

Drug Class: Immunosuppressant and immunomodulator.

Indication: [redacted]

Clinical formulation:

Cyclosporine, USP, 0.05% or 0.1% w/w
Castor oil PhEur, [redacted]
Polysorbate 80 NF
Carbomer 1342 NF
Glycerine USP,
Sodium hydroxyide USP,
Purified water USP,

Route of administration: Topical, instilled in eyes.

Proposed clinical use: The ophthalmic emulsion will be used topically for the treatment of KCS.

The proposed dose is: Ophthalmic drops 0.05% Cyclosporine, one drop in each eye, twice a day approximately 12 hours apart

Disclaimer: The sponsor submitted a letter of authorization from Novartis dated April 27, 1998 for cross-referencing all Cyclosporine INDs and NDAs.

Introduction and drug history:

Cyclosporine (CSA) is a cyclic polypeptide extracted from the fungus Beauveria nivea. It is an immunosuppressive agent approved for the treatment of the rejection of organ transplants, rheumatoid arthritis and psoriasis. Cyclosporine 0.2% ophthalmic ointment is approved for the treatment of chronic KCS in dogs. It CSA has also been investigated for several autoimmune and inflammatory diseases of the eye e.g. uveitis and Behcet's disease etc. The mode of action of CSA is through the inhibition of release of several cytokines e.g. IL-2, IL-3, IL-4, INF, GM-CSF and TNF. Most recently CSA has been shown to increase the transcription of TGF-β. In the present NDA the sponsor submitted study reports for the efficacy and safety of CSA for the treatment of keratoconjunctivitis sicca (dry eye) with or without Sjogren syndrome. Dry eye conditions result from reduced secretion of the tear from acinar epithelial cells in the eye. Experimental studies shown that invasion of T lymphocytes in the secretory gland affect the function of acinar epithelial.

The sponsor proposed that the local application of CSA would inhibit the T lymphocyte functions, reduce apoptosis of the epithelial, improve and restore the tear secretion.

Pharmacology:

The sponsor has submitted literature citations on the mechanism of actions of Cyclosporine and its effects in KCS in animal models. Summaries of some of these citations are presented in the review. However, the reviewer does not agree with the efficacy claims in the published papers for the indications not approved by the Agency.

Mechanism of action:

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The sponsor referred to several published papers on the immunosuppressive effect of Cyclosporine (CSA). However, the review written by Borel et al. Adv. Pharmacology 35, 115 provided a detailed analysis of its mode of action. CSA inhibits both humoral and cell mediated immunity. It is effective in chronic immune mediated inflammatory conditions and inhibition of graft rejection. The effect of CSA has been demonstrated in several inflammatory conditions including autoimmune uveitis, psoriasis, idiopathic nephrotic syndrom and rheumatoid arthritis.

CSA inhibits the function of T- lymphocytes without affecting the function of phagocytes or hemopoietic stem cells. The mechanism of CSA involves inhibition of cytokine release from the helper T cells. CSA binds with cytosolic protein known as cyclophilin. The CSA-cyclophilin complex inhibits calcium calmodulin-dependent protein calcineurine. Inhibition of calcineurine phosphatase activity by CSA-cyclophilin complex contributes to the inhibition of the function transcription factors e.g. NFAT and NFκB. The inhibition of the nucleotide regulatory factors results in the down regulation of the cytokine gene expression. CSA also has antagonistic effect on prolactin. It is suggested that inhibition of prolactin contribute to the antiinflammatory effect of CSA.

Drug activity related to proposed indication:

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The sponsor cited several published Papers on the effect of CSA in KCS in animals.

1. Role of apoptosis in the pathogenesis of canine keratoconjunctivitis sicca: The effect of topical Cyclosporine A therapy. Gao et al. Cornea, 17 (6), 654-663, 1998.

The authors stated that T lymphocytic infiltration was detected in the biopsies of lacrimal glands of dogs with spontaneous chronic idiopathic KCS. Apoptosis of the lymphocytes, lacrimal acinar epithelial and conjunctival epithelial cells were evaluated in spontaneous idiopathic KCS in dogs. The role of CSA in the apoptosis process has been discussed. Dogs that were clinically diagnosed with KCS were enrolled. Ten dogs with KCS were treated

with 0.2% CSA ophthalmic emulsion, three dogs with KCS were treated with the vehicle and another four normal dogs were used as the baseline control. Treated animals were dosed with one drop of CSA or the vehicle in each eye twice a day for 13 weeks. Lubricant eyedrops were applied at noon between the treatments. For the biopsy procedures, dogs were treated with atropine subcutaneously, anesthetized with i.v injections of Valium and Ketamine and treated with topical proparacaine. Doses of the treatment have not been mentioned. Biopsy specimens were obtained from the lacrimal glands and conjunctiva before and after 13 weeks of the treatment. Apoptotic cells were labelled and examined under light microscope. The apoptotic process was confirmed by DNA fragmentation analysis. Furthermore, monoclonal antibodies against fas-ligand, polyclonal antibodies against fas-ligand and monoclonal antibody against bcl-2 expressed proteins were used to show distribution of apoptotic receptor sites in the cell. Results indicated that the vehicle treated dogs had increase in the apoptosis of acinar, conjunctival epithelial cells and decrease in the apoptosis of the lymphocytes when compared to the normal dogs. The process was reversed after the treatment with CSA topically. It was concluded that suppression of apoptosis of lymphocytes and induction of apoptosis of epithelial cells of lacrimal glands and conjunctiva were the characteristic features of KCS in dogs. CSA treatment modulated the apoptic process.

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2. The sponsor has provided a review on KCS in dogs and the effect of CSA. The review was published by Kaswan and Salisbury, Vet clinics of North America, 20, 583, 1990. The review provided information covered by the citation described above. In addition, the review addressed the issue that the effect of CSA could be due to the irritant property of the drug. However, commonly known irritants are not effective in treating KCS. Therefore, the pharmacodynamic effect of CSA in KCS is not likely to be mediated by the irritant effect of CSA. The article also discussed about the opportunistic infections in the cornea and conjunctiva. However, the risk may be similar to corticosteroids. The issue of bioavailability of CSA in the lacrimal gland was raised in the publication. However, data on the CSA level in the lacrimal gland have not been provided.

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3. Characteristics of a canine model of KCS: effective treatment with topical Cylosporine. By Kaswan. Lacrimal gland, tear film and dry eye syndromes, Edited by D.A. Sullivan, Plenum Press, N.Y 1994.

The review stated the mode of action of CSA for the treatment of KCS is as follows.

a. Modulation of cytokine production in the lacrimal gland.
b. Decreased recruitment of auto reactive lymphocytes from the conjunctiva to the lacrimal gland.
c. A direct neurohormonal effect of CSA mediated through prolactin receptors identified on lacrimal acinar epithelium. Prolactin is considered to be a natural ligand for cyclophilin. However, role of prolactin receptor in the lacrimal gland and its relationship to the effect of CSA is not clearly known.

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