DESCRIPTION

RESTASIS™ (cyclosporine opthalmic emulsion) 0.05% contains a topical immunomodulator with anti-inflammatory effects. Cyclosporine’s chemical name is Cyclosporin (E)-(Z)-(3,4,9)-3-hydroxy-4-methyl-2-(methylamin)-6-oxocyclohexyl-L-2-aminoisobutryl-N-methylglycol-4-N-methyl-L-tyrosyl-L-valyl(4-N-methyl-L-tyrosyl-L-alanyl-D-alanyl-N-methyl-L-tyrosyl-N-methyl-L-leucyl-N-methyl-L-valyl) and it has the following structure:

Structural Formula

Formula: C_{18}H_{30}N_{7}O_{6}
Mol. Wt.: 11202.6

Cyclosporine is a fine white powder. RESTASIS™ appears as a white opaque to slightly translucent homogeneous emulsion. It has an osmolality of 230 to 320 mOsm/kg and a pH of 6.5-8.0. Each ml of RESTASIS™ contains:

Active: cyclosporine 0.05%,
Inactive: glycine/Na citrate; polysorbate 80; carborner 1342; purified water and sodium hydroxide to adjust the pH.

CLINICAL PHARMACOLOGY

Mechanism of action: Cyclosporine is an immunosuppressant agent when administered systemically. In patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca, cyclosporine emulsion is thought to act as a partial immunomodulator. The exact mechanism of action is not known.

Pharmacokinetics:
Blood cyclosporin A concentrations were measured using a specific high pressure liquid chromatography–mass spectrometry assay. Blood concentrations of cyclosporine, in all the samples collected, after topical administration of RESTASIS™ 0.05%, BID, in humans for up to 12 months, were within the below quantity limit of 0.1 ng/mL. There was no detectable drug accumulation in blood during 12 months of treatment with RESTASIS™.

Carcinogenesis, Mutagenesis, and Impairment of Fertility:
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 0.05% RESTASIS™ BID into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed.

Cyclosporine has not been found mutagenic/genotoxic in the Ames Test, the V79-HPRT 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).

No impairment in fertility was demonstrated in studies in male and female rats receiving oral doses of cyclosporine up to 15 mg/kg/day (approximately 15,000 times the human daily dose of 0.001 mg/kg/day) for 9 weeks (male) and 2 weeks (female) prior to mating.

Pregnancy-Teratogenic effects:
Pregnancy category C.

Non-Teratogenic effects: Adverse effects were seen in reproduction studies in rats and rabbits only at doses 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 and 100,000 times greater, respectively, than the daily human dose of one drop (28 µL) of 0.05% RESTASIS™ BID into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed.

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

There are no adequate and well-controlled studies of RESTASIS™ in pregnant women. RESTASIS™ should be administered to pregnant women only if clearly needed.

Nursing Mothers:
Cyclosporine is known to be excreted in human milk following systemic administration but excretion in milk after topical treatment has not been investigated. Although blood concentrations are undetectable after topical administration of RESTASIS™, caution should be exercised when RESTASIS™ is administered to a nursing woman.

Pediatric Use:
The safety and efficacy of RESTASIS™ have not been established in pediatric patients below the age of 16.

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

ADVERSE REACTIONS

The most common adverse event following the use of RESTASIS™ was ocular burning (17%). Other events reported in 1% to 5% of patients included conjunctival hyperemia, discharge, epiphora, eye pain, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).

DOSAGE AND ADMINISTRATION

Invert the unit dose vial a few times to obtain a uniform, white, opaque emulsion before using. Instill one drop of RESTASIS™ twice a day in each eye approximately 12 hours apart. RESTASIS™ can be used concomitantly with artificial tears, allowing a 15 minute interval between products. Discard vial immediately after use.

HOW SUPPLIED

RESTASIS™ is packaged in single use vials. Each vial contains immediate use 0.4 mL, fill to 0.9 mL. LDPE vial; 32 vials are packaged in a polypropylene tray with an aluminum peelable lid.

Storage: Store RESTASIS™ below 25°C.

KEEP OUT OF REACH OF CHILDREN.

Rx Only
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