2464

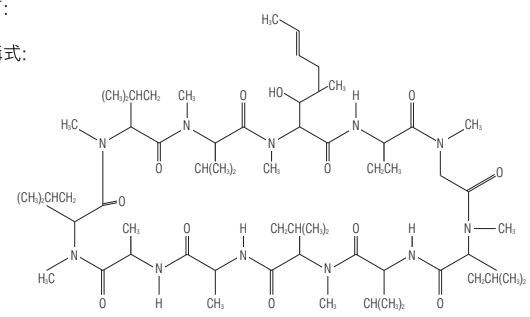
“愛力根”麗眼達®眼用乳劑 0.05%
RESTASIS® Ophthalmic Emulsion 0.05%

衛署藥輸字第024206號

性狀

RESTASIS®（環孢靈眼用乳劑）0.05%含有抗炎作用之局部免疫調節劑。Cyclosporine的化學名是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，其結構式如下:

結構式:



化學式：$C_{62}H_{111}N_{11}O_{12}$　　分子量：1202.6

Cyclosporine是白色細粉，RESTASIS®為白色不透明至略為半透明之均質乳劑，具有滲透壓230至320 mOsmol/kg和pH值6.5-8.0。

每一mL RESTASIS®眼用乳劑含有活性成分：cyclosporine 0.05%，非活性成分：甘油（glycerin）、蓖麻油（castor oil）、polysorbate 80、carbomer 1342、純水和氫氧化鈉用來調整pH值。

臨床藥理學

作用機轉：

Cyclosporine於全身性投藥時是作為免疫抑制劑。

用於與乾性角膜結膜炎（keratoconjunctivitis sicca）有關聯的發炎作用，造成淚液分泌減少的病患，cyclosporine乳劑可作為局部免疫調節劑，但確切的作用機轉未明。

藥動學方面:

血中cyclosporin A濃度係使用特定高壓液相層析儀-質譜儀檢定分析測量，人體長達12個月局部投予RESTASIS® 0.05% 每日兩次，後收集得之檢體中，cyclosporine血中濃度全部皆低於0.1 ng/mL之定量極限。使用RESTASIS®眼用乳劑治療12個月期間，血液中未偵測得任何藥物積聚的濃度。

臨床評估:

使用約1200位患有中度至重度乾性角膜結膜炎病患，進行四項多中心且隨機分配的，經過適當良好對照組對照的臨床研究，RESTASIS®用於經推定淚液產量減少，係由於眼部發炎所引起的病患，六個月時Schirmer濕潤度增加10 mm者，相較於媒劑組顯示，於統計學上呈現有意義的增加；此種效果係出現於約15%接受RESTASIS®眼用乳劑治療病患，相較於約5%接受媒劑治療的病患。但目前正在使用局部抗炎藥物，或使用淚點塞(punctal plugs)的病患，未出現淚液產量增加的現象。

投與RESTASIS®後，未曾有任何眼部細菌性感染或黴菌感染增加的報告。

適應症

治療嚴重乾性角結膜炎（Schirmer test without anesthesia < 5mm/5min）併角結膜上皮病變患者之發炎反應，但在目前使用局部抗發炎藥物或使用淚點塞病患未見療效者。

禁忌

RESTASIS®禁忌用於目前有眼部感染，和已知或懷疑對本品處方中的任一種成分過敏病患。

警語

RESTASIS®眼用乳劑未曾針對有皰疹性角膜炎病史之病患作研究。

注意事項

一般注意事項：限供眼部使用。

病患資訊：

每瓶限單次使用，小瓶中的乳劑須在開封後即刻點於單眼或雙眼，剩餘藥液須於投藥後即刻拋棄。

不要讓藥瓶尖端接觸到眼球或任何其它表面，以免因此而使乳劑受到污染。
RESTASIS®禁忌於佩戴隱形眼鏡狀態下投藥，淚液產量不足病患一般也不應佩戴隱形眼鏡；若有佩戴隱形眼鏡，須在本品投藥前取下隱形眼鏡，等RESTASIS®眼用乳劑投藥後15分鐘，再重新戴上隱形眼鏡。

致癌性、致突變性、與生育力受損：

對雄性和雌性大鼠和小鼠進行全身性致癌作用研究，每日以1、4及16 mg/kg劑量進行為期78週的經口攝食小鼠研究，雌鼠發生淋巴性淋巴腫瘤有統計學上顯著的趨勢，中等劑量組的雄鼠之肝細胞癌發生率超過對照組的數值。

每日使用0.5、2及8 mg/kg劑量進行為期24個月的經口攝食大鼠研究中，胰島細胞腺癌發生率顯著超越使用較低劑量之對照組，肝細胞癌和胰島細胞腺癌之發生率與劑量並無相關性。假設全部劑量皆被身體所吸收，於小鼠和大鼠使用的低劑量分別比人類60公斤成人雙眼每日兩次，各滴一滴（28 µL）0.05% RESTASIS®（0.001 mg/kg/day）劑量高約1,000倍和500倍。

Cyclosporine在下列各項實驗皆未見突變性/基因毒性：Ames試驗、V79-HGPRT突變分析；在小鼠和中國倉鼠的微核試驗、中國倉鼠骨髓的染色體變異試驗、小鼠顯性致死試驗、和得自處理組小鼠精蟲之DNA修復試驗。使用人類淋巴細胞分析cyclosporine對姊妹染色體交換(SCE)體外試驗分析研究，顯示為陽性結果(換言之具SCE誘導作用)。

利用雄大鼠和雌大鼠於交配前接受高達15 mg/kg/day cyclosporine（約為人用每日劑量0.001 mg/kg/day之約15,000倍）口服劑量長達9週（雄大鼠）和2週（雌大鼠）之研究，證實cyclosporine不會對生育力造成損害。

用於孕婦致畸胎效應：

孕婦用藥級數：C級。

致畸胎作用：大鼠或兔接受高達300 mg/kg/day cyclosporine口服劑量，於器官形成期未出現任何致畸胎作用證據，假設全部劑量皆被身體所吸收，大鼠和兔子之使用劑量比60公斤成人雙眼每日兩次，各滴一滴（28 µL）0.05% RESTASIS®的人用劑量高約300,000倍。

非致畸胎作用：於大鼠和兔之生殖研究中，唯有在對母體有毒之劑量才會出現不良影響，於cyclosporine口服液劑，USP中毒劑量(大鼠為30 mg/kg/day以及兔為100 mg/kg/day)，cyclosporine口服液劑具有胚毒性和胎毒性，由產前和產後死亡率增高以及胚胎體重減輕，連帶骨骼發育延遲可證；假設全部劑量皆被吸收，使用劑量分別比60公斤成人雙眼每日兩次，各滴一滴(28 µL) 0.05% RESTASIS®的人用劑量高約30,000倍及100,000倍。於器官形成期，大鼠或兔分別接受高達17 mg/kg/day或30 mg/kg/day口服劑量之cyclosporine，未觀察得任何胚胎毒性證據，此種劑量分別比每日人體劑量高約17,000和30,000倍。

雌大鼠於妊娠第15日至產後第21日，接受45 mg/kg/day cyclosporine對母體為中毒濃度之口服劑量，該雌大鼠產下的小鼠顯示產後死亡率增高；假設全部劑量皆被吸收，這種劑量比每日人類局部劑量0.001 mg/kg/day高45,000倍；於高達15 mg/kg/day口服劑量（比每日人類劑量高15,000倍）未觀察得任何不良影響。

RESTASIS®尚未於孕婦進行充分且有良好對照組之臨床研究。

RESTASIS®唯有在有明確需要時才可以用於孕婦。

哺乳婦：

Cyclosporine已知於全身性投藥後會分泌於人類乳汁，但未曾進行局部治療是否會分泌於人類乳汁的研究；雖然局部投予RESTASIS®眼用乳劑後血中濃度偵測不到，但RESTASIS®投予哺乳婦時應審慎。

用於兒童：

RESTASIS®眼用乳劑用於16歲以下兒童病人的安全性及療效尚未明確建立。

用於老人：

老年病人與年輕病人間並未觀察到安全性或療效之差異。

不良反應

使用RESTASIS®後最常見的不良影響是眼部燒灼感（17%）。
其它不良反應發生率報告介於1%至5%者，包括結膜充血、分泌物增加、溢淚、眼痛、異物感、搔癢、刺痛及視覺障礙（最常見者為視覺模糊）。

用法用量：本藥須由醫師處方使用

本藥為局部點眼藥，每日使用兩次，間隔約12小時。使用前，將單位劑量小瓶上下顛倒數次，形成均勻白色不透明乳液後，於雙眼各滴一滴RESTASIS®眼用乳劑，RESTASIS®可合併人工淚液使用，但使用兩種藥品應間隔15分鐘。使用後即刻拋棄該小瓶。

包裝

RESTASIS®眼用乳劑，單次使用小瓶包裝，每小瓶為0.4 mL填裝於0.9 mL LDPE小瓶；30小瓶放在一片聚丙烯托盤上，附上可撕離的鋁蓋包裝，整個托盤(30小瓶)為一個出售單位。

RESTASIS®：30小瓶裝。

儲存：儲存於15°C至25°C（59 -77°F）。
置於兒童不能及之處。

製造廠
Allergan Sales, LLC
8301 Mars Drive, Waco
Texas 76712, U.S.A.

藥商
香港商愛力根有限公司台灣分公司
台北市羅斯福路二段102號 9樓

INSERT, STANDARDIZED,
8-1/4" X 14"
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- Part number: 72217UT10A
- Drawing Number: 0284201
- V-Code: 2464
- Artwork is actual size
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- Page 1 of 2

ALLERGAN®

RESTASIS®

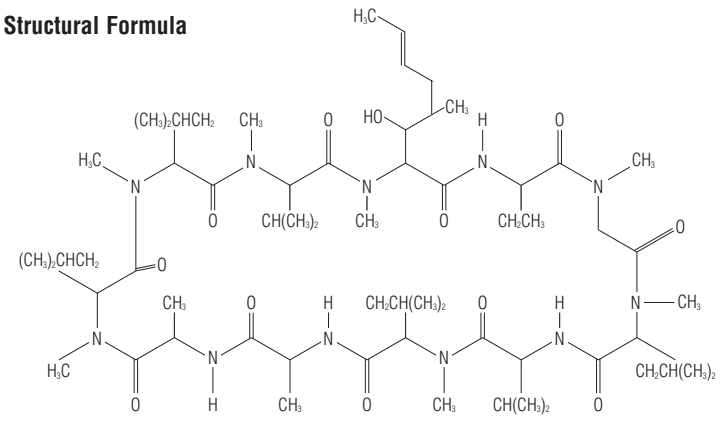
(cyclosporine ophthalmic emulsion) 0.05%

Sterile, Preservative-Free

DESCRIPTION

RESTASIS® (cyclosporine ophthalmic emulsion) 0.05% contains a topical immunomodulator with anti-inflammatory effects. Cyclosporine's chemical name is 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] and it has the following structure:

Structural Formula



Formula: $C_{62}H_{111}N_{11}O_{12}$ Mol. Wt.: 1202.6

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 mOsmol/kg and a pH of 6.5-8.0.

Each mL of RESTASIS® contains: **Active:** cyclosporine 0.05%. **Inactive:** glycerin; castor oil; polysorbate 80; carbomer 1342; purified water and sodium hydroxide to adjust the pH.

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 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 below the quantitation limit of 0.1 ng/mL. There was no detectable drug accumulation in blood during 12 months of treatment with RESTASIS®.

Clinical Evaluations:

Four multicenter, randomized, adequate and well-controlled clinical studies were performed in approximately 1200 patients with moderate to severe keratoconjunctivitis sicca. RESTASIS® demonstrated statistically significant increases in Schirmer wetting of 10 mm versus vehicle at six months in patients whose tear production was presumed to be suppressed due to ocular inflammation. This effect was seen in approximately 15% of RESTASIS® treated patients versus approximately 5% of vehicle treated patients. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

No increase in bacterial or fungal ocular infections was reported following administration of RESTASIS®.

INDICATIONS AND USAGE

RESTASIS® is indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca. Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

CONTRAINDICATIONS

RESTASIS® is contraindicated in patients with active ocular infections and in patients with known or suspected hypersensitivity to any of the ingredients in the formulation.

WARNING

RESTASIS® has not been studied in patients with a history of herpes keratitis.

PRECAUTIONS

General: For ophthalmic use only.

Information for Patients:

The emulsion from one individual single-use vial is to be used immediately after opening for administration to one or both eyes, and the remaining contents should be discarded immediately after administration.

Do not allow the tip of the vial to touch the eye or any surface, as this may contaminate the emulsion.

RESTASIS® should not be administered while wearing contact lenses. Patients with decreased tear production typically should not wear contact lenses. If contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted 15 minutes following administration of 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-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).

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.

Teratogenic effects: No evidence of teratogenicity was observed in rats or rabbits receiving oral doses of cyclosporine up to 300 mg/kg/day during organogenesis. These doses in rats and rabbits are approximately 300,000 times greater than the daily human dose of one drop (28 µl) 0.05% RESTASIS® BID into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed.

Non-Teratogenic effects: Adverse effects were seen in reproduction studies in rats and rabbits 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 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. No evidence of embryofetal toxicity was observed in rats or rabbits receiving cyclosporine at oral doses 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.

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 systematic 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 0.4 mL fill in a 0.9 mL LDPE vial; 30 vials are packaged in a polypropylene tray with an aluminium peelable lid.

Storage: Store RESTASIS® below 25°C.

KEEP OUT OF REACH OF CHILDREN.

Rx Only

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Allergan Sales, LLC
Waco, TX 76712
U.S.A.

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