

021 023\_Original Approval\_Package.pdf

# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

*APPLICATION NUMBER:*

**21-023**

*Trade Name:* Restasis

*Generic Name:* Cyclosporine ophthalmic emulsion, 0.05%

*Sponsor:* Allergan, Inc.

*Approval Date:* October 10, 2003

*Indications:* Provides for the use of Restasis (cyclosporine ophthalmic emulsion) Ophthalmic Emulsion, 0.05% for the following indication: 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.

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**21-023**

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### **Reviews / Information Included in this NDA Review.**

<b>Approval Letter</b>	<b>X</b>
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<b>Final Printed Labeling</b>	<b>X</b>
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<b>EA/FONSI</b>	
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<b>Correspondence</b>	

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-023**

**APPROVAL LETTER(S)**



NDA 21-023

Allergan, Inc.  
Attention: Elizabeth Bancroft  
Senior Director, Regulatory Affairs  
2525 Dupont Drive  
P.O. Box 19534  
Irvine, California 92623-9534

Dear Ms. Bancroft:

Please refer to your new drug application (NDA) dated February 24, 1999, received February 25, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Restasis (cyclosporine ophthalmic emulsion) Ophthalmic Emulsion, 0.05%.

We acknowledge receipt of your submissions dated September 7, 2001, and April 23, May 22, June 17, July 11, September 6, October 28, November 15, and December 4, 6, 16 and 20, 2002.

We also refer to our approvable letters of August 3, 1999, and March 25, and October 19, 2000. The September 6, 2002, submission constituted a complete response to our October 19, 2000, action letter.

This new drug application provides for the use of Restasis (cyclosporine ophthalmic emulsion) Ophthalmic Emulsion, 0.05% for the following indication: 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.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling text for the package insert, immediate container and carton labels. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "FPL for approved NDA 21-023." Approval of this submission by FDA is not required before the labeling is used.

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Page 2

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We have not completed validation of the regulatory methods. However, we expect your continued cooperation to resolve any problems that may be identified.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Lori M. Gorski, Project Manager, at (301) 827-2090.

Sincerely,

*{See appended electronic signature page}*

Wiley A. Chambers, M.D.  
Deputy Director  
Division of Anti-Inflammatory, Analgesic  
and Ophthalmic Drug Products, HFD-550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

Enclosure

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-023**

**APPROVABLE LETTER(S)**

Food and Drug Administration  
Rockville MD 20857

OCT 19 2000

NDA 21-023

Allergan, Inc.  
Attention: Elizabeth Bancroft  
Director, Regulatory Affairs  
2525 Dupont Drive  
P.O. Box 19534  
Irvine, California 92623-9534

Dear Ms. Bancroft:

Please refer to your new drug application (NDA) dated February 24, 1999, received February 25, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Restasis (cyclosporine ophthalmic emulsion) Ophthalmic Emulsion, 0.05%.

We acknowledge receipt of your submissions dated April 24, August 9, 22, 23, and 31, September 7, and October 2 and 3, 2000. We also refer to our approvable letters of August 3, 1999, and March 25, 2000. Your submission of August 9, 2000, constituted a complete response to our March 25, 2000, action letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the lack of substantial evidence of efficacy. Substantial evidence should consist of adequate and well-controlled investigations, as defined in 21 CFR 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the proposed labeling. Specifically, the submitted studies are not replicative and are insufficient to establish efficacy

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug.

We will continue to work with you on the proposed labeling for this product.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this Division to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Lori M. Gorski, Project Manager, at (301) 827-2090.

Sincerely,

  
Wiley A. Chambers, M.D.  
Deputy Director  
Division of Anti-Inflammatory, Analgesic and  
Ophthalmic Drug Products, HFD-550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

cc:

NDA 21-023

HFD-550/Div. Files

Initialed by:

HFD-550/CSO/Gorsk *LSI*

*LSI*

HFD-550/MO/Boyd *LSI*

HFD-550/Chem/Tsu *LSI*

HFD-550/Phar/Mukherjee

HFD-725/Stat/Lu *LSI*

HFD-880/PK/Tandon

HFD-805/Micro/Riley

HFD-550/DepDir/Chambers

HFD-550/ADD/Bull *LSI*

HFD-550/SCSO/Vacc&tr. *LSI*

HFD-550/ChemTL/Ng *LSI*

HFD-725/Stat TL/Lin *LSI*

HFD-880/PK TL/Bashaw *LSI*

HFD-805/Micro TL/Cooney

HFD-002/ORM

HFD-105/ADRA

HFD-95/DDMS

HFD-830/DNDC Division Director

DISTRICT OFFICE

Drafted by: /October 12, 2000. revised 10/16/00

Initialed by:

final: *LSI*

filename:

APPROVABLE (AE)

Food and Drug Administration  
Rockville MD 20857

NDA 21-023

MAR 25 2000

Allergan, Inc.  
Attention: Elizabeth Bancroft  
Director, Regulatory Affairs  
2525 Dupont Drive  
P.O. Box 19534  
Irvine, California 92623-9534

Dear Ms. Bancroft:

Please refer to your new drug application (NDA) dated February 24, 1999, received February 25, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Restasis (cyclosporine ophthalmic emulsion) Ophthalmic Emulsion, 0.05%.

We acknowledge receipt of your submissions dated August 4 (two), September 3 and 20, and December 8, 1999. Your submission of December 8, 1999, constituted a complete response to our August 3, 1999, action letter.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

1. There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 21 CFR 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the proposed labeling. Specifically, the submitted studies are not replicative and are insufficient to establish efficacy
2. Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug.

We will continue to work with you on the proposed labeling for this product.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this Division to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Lori M. Gorski, Project Manager, at (301) 827-2090.

Sincerely,



Wiley A. Chambers, M.D.  
Deputy Director  
Division of Anti-Inflammatory, Analgesic  
Ophthalmic Drug Products, HFD-550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

cc:

NDA 21-023

HFD-550/Div. Files

HFD-550/CSO/Gorsk

HFD-550/MO/Boyd

HFD-550/Chem/Fenselau

HFD-550/Phar/Mukherjee

HFD-725/Stat/Lu

HFD-880/PK/Tandon

HFD-805/Micro/Riley

HFD-550/DepDir/Chambers

HFD-550/DD/Midthun

HFD-550/SCSO/Vaccari

HFD-550/ChemTL/Ng

HFD-725/Stat TL/Lin

HFD-880/PK TL/Bashaw

HFD-805/Micro TL/Cooney

HFD-002/ORM

HFD-105/ADRA

HFD-95/DDMS

HFD-830/DNDC Division Director

DISTRICT OFFICE

LSI

Drafted by: /March 15, 2000

Initialed by: \_\_\_\_\_

APPROVABLE (AE)

LSI



NDA 21-023

AUG 3 1999

Allergan, Inc.  
Attention: Elizabeth Bancroft  
Director, Regulatory Affairs  
2525 Dupont Drive  
P.O. Box 19534  
Irvine, California 92623-9534

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We acknowledge receipt of your submissions dated February 24, March 2, 3, 18, and 30, April 7, 20, 22, and 23, May 5, 10 (three), and 28, June 17, and July 8, 12, 13, 16 and 26, 1999.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

1. There is a lack of substantial evidence consisting of adequate and well-controlled investigations, as defined in 21 CFR 314.126, that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended or suggested in the proposed labeling. Specifically, the submitted studies are not replicative and are insufficient to establish efficacy in the \_\_\_\_\_.
2. The methods to be used in, and the facilities and controls used for, the manufacture, processing, packing or holding of the drug substance or the drug product are inadequate to preserve its identity, strength, quality, purity, stability and bioavailability. Specifically, the following issues will need to be addressed:
  - a. The limit of \_\_\_\_\_ for \_\_\_\_\_ appears high for a sterile product. Please provide justification for using this limit.
  - b. The \_\_\_\_\_ test data was not included. Please provide the data for the container/closure \_\_\_\_\_ test.

- c. With regard to the performance qualification of the \_\_\_\_\_ machine and the verification of the \_\_\_\_\_ please provide the data from the original qualification performed using \_\_\_\_\_
- d. \_\_\_\_\_ were not included in the \_\_\_\_\_ during the \_\_\_\_\_ validation. Therefore, the effect of the \_\_\_\_\_ on the \_\_\_\_\_ has not been established. Please provide information to demonstrate that a \_\_\_\_\_ will be sufficient to \_\_\_\_\_
- e. The study performed to validate a \_\_\_\_\_ for the drug product does not support \_\_\_\_\_

We will continue to work with you on the proposed labeling for this product.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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Office of Drug Evaluation V  
Center for Drug Evaluation and Research

cc:

NDA 21-023

HFD-550/Div. Files

HFD-550/CSO/Gorski

HFD-550/MO/Boyd

HFD-550/Chem/~~Boyd~~

HFD-550/Phar/Mukherjee

HFD-725/Stat/Lu

HFD-880/PK/Tandon

HFD-805/Micro/Riley

HFD-550/DepDir/Chambers

HFD-550/ChemTL/Ng

HFD-550/Pharm TL/Weir

HFD-550/Clin Rev/Holmes

HFD-725/Stat TL/Lin

HFD-880/PK TL/Bashaw

HFD-805/Micro TL/Cooney

HFD-002/ORM

HFD-105/ADRA

HFD-95/DDMS

HFD-830/DNDC Division Director

DISTRICT OFFICE

Drafted by: /July 28, 1999

filename: 21023AE.WPD

APPROVABLE (AE)

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