

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

50790Orig1s25

Trade Name: **RESTASIS MULTIDOSE**

Generic or Proper Name: **cyclosporine**

Sponsor: **Allergan Inc.**

Approval Date: **October 27, 2016**

Indication: RESTASIS MULTIDOSE is a calcineurin inhibitor immunosuppressant indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.

CENTER FOR DRUG EVALUATION AND RESEARCH

50790Orig1s25

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50790Orig1s25

APPROVAL LETTER



NDA 50790/S-024
NDA 50790/S-025

SUPPLEMENT APPROVAL

Allergan, Inc.
Attention: Linda McCauley, PhD
Manager, Global Regulatory Affairs
2525 Dupont Drive
PO Box 19534
Irvine, CA 92623-9534

Dear Dr. McCauley:

Please refer to your Supplemental New Drug Applications (sNDA) dated November 3, 2015, received November 3, 2015, and your amendments, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for RESTASIS MULTIDOSE™ (cyclosporine ophthalmic emulsion) 0.05%.

Supplement 024 proposes adding a Multi-Dose (b) (4) Container Closure System. Supplement 025 proposes adding labeling for the Multi-Dose (b) (4) Container Closure System. It also provides for conversion of Section 8 to Pregnancy and Lactation Labeling (PLLR) format and proposes changes to Section 13.

APPROVAL & LABELING

We have completed our review of these two supplemental applications, as amended. They are both approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert) with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REPORTING REQUIREMENTS

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 Jacquelyn Smith, MA, Senior Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Deputy Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE(S):

Content of Labeling
Carton and Container Labeling

**CENTER FOR DRUG EVALUATION AND
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APPLICATION NUMBER:

50790Orig1s25

OTHER ACTION LETTERS



NDA 50790/S-025

COMPLETE RESPONSE

Allergan, Inc.
Attention: Kathrin Schalper, PhD, RAC, PMP
Senior Manager, Global Regulatory Affairs
2525 Dupont Drive
Irvine, CA 92612

Dear Dr. Schalper:

Please refer to your Supplemental New Drug Application (sNDA) dated November 3, 2015, received November 3, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for RESTASIS® (cyclosporine ophthalmic emulsion) 0.05%.

This supplemental new drug application proposes to add labeling for a Multi-Dose (b) (4) Container Closure System. It also provides for conversion of Section 8 to Pregnancy and Lactation Labeling (PLLR) format and proposes changes to Section 13. We have completed the review of your package insert, as amended, and have determined that we cannot approve your labeling in its present form. We are providing our proposed revisions in the attached labeling.

Specifically, we have removed all references to the Multi-Dose (b) (4) Container Closure System because this system is unapproved.

Section 8 USE IN SPECIFIC POPULATIONS and Section 13 NONCLINICAL TOXICOLOGY have been revised as indicated in the attached labeling.

Editorial revisions have also been made in Section 2 DOSAGE AND ADMINISTRATION and Section 6 ADVERSE REACTIONS.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Submit draft labeling that addresses our proposed revisions in the attached labeling.

Prior to resubmitting the labeling, use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. In addition, submit updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Word version. The marked-up copy should include annotations that support any proposed changes.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry, “Formal Meetings Between FDA and Sponsors or Applicants,” May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

If you have any questions, call Jacquelyn Smith, MA, Senior Regulatory Project Manager, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Deputy Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE(S):
Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILEY A CHAMBERS
05/02/2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50790Orig1s25

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use RESTASIS MULTIDOSE™ safely and effectively. See full prescribing information for RESTASIS MULTIDOSE™.

RESTASIS MULTIDOSE™ (cyclosporine ophthalmic emulsion) 0.05%

For topical ophthalmic use

Initial U.S. Approval: 1983

INDICATIONS AND USAGE

RESTASIS MULTIDOSE™ is a calcineurin inhibitor immunosuppressant 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. (1)

DOSAGE AND ADMINISTRATION

- Prime by squeezing two drops onto a tissue before initial use. (2.1)
- Instill one drop of RESTASIS MULTIDOSE™ ophthalmic emulsion twice a day in each eye approximately 12 hours apart. (2.2)

DOSAGE FORMS AND STRENGTHS

Cyclosporine ophthalmic emulsion 0.5 mg/mL (3)

CONTRAINDICATIONS

- Hypersensitivity (4)

WARNINGS AND PRECAUTIONS

- To avoid the potential for eye injury and contamination, be careful not to touch the bottle tip to your eye or other surfaces. (5.1)

ADVERSE REACTIONS

The most common adverse reaction following the use of cyclosporine ophthalmic emulsion 0.05% was ocular burning (17%). (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Allergan, Inc. at 1-800-433-8871 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2016

FULL PRESCRIBING INFORMATION: CONTENTS***1 INDICATIONS AND USAGE****2 DOSAGE AND ADMINISTRATION**

2.1 Preparation for First-Time Use

2.2 Preparation for Use

3 DOSAGE FORMS AND STRENGTHS**4 CONTRAINDICATIONS****5 WARNINGS AND PRECAUTIONS**

5.1 Potential for Eye Injury and Contamination

5.2 Use with Contact Lenses

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12.1 Mechanism of Action

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13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES**16 HOW SUPPLIED/STORAGE AND HANDLING****17 PATIENT COUNSELING INFORMATION**

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

RESTASIS MULTIDOSE™ ophthalmic emulsion 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.

2 DOSAGE AND ADMINISTRATION

Instill one drop of **RESTASIS MULTIDOSE™** ophthalmic emulsion twice a day in each eye approximately 12 hours apart. **RESTASIS MULTIDOSE™** can be used concomitantly with lubricant eye drops, allowing a 15-minute interval between products.

2.1 Preparation for First-Time Use

Step 1: Pull off the clear shipping cover by pulling straight up. Throw the shipping cover away.

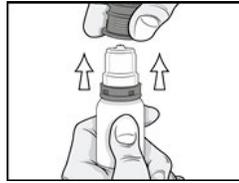


Do not use **RESTASIS MULTIDOSE™** if shipping cover or pull tab are damaged or missing.

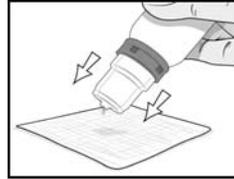
Step 2: Remove the pull tab on the olive green colored protective cap by pulling the end of the pull tab away from the bottle then winding it counterclockwise. Throw away the pull tab.



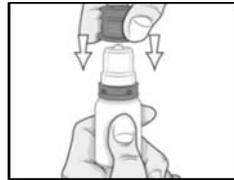
Step 3: Remove the olive green colored protective cap by pulling it straight up. Keep the colored protective cap.



Step 4: Prime the bottle for first-time use by squeezing two drops onto a tissue. Do not let the bottle tip touch the tissue.

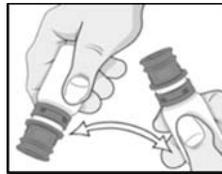


Step 5: The bottle is now ready for use. After use, recap the bottle with the olive green colored protective cap by pushing it straight down onto the bottle.



2.2 Preparation for Use

Step 6: Turn the bottle upside down a few times before giving your dose to make sure the medicine is mixed well.



Step 7: Instill one drop in the affected eye. Replace the olive green colored protective cap.

3 DOSAGE FORMS AND STRENGTHS

Ophthalmic emulsion containing cyclosporine 0.5 mg/mL

4 CONTRAINDICATIONS

RESTASIS MULTIDOSE™ is contraindicated in patients with known or suspected hypersensitivity to any of the ingredients in the formulation [*see Adverse Reactions (6.2)*].

5 WARNINGS AND PRECAUTIONS

5.1 Potential for Eye Injury and Contamination

Be careful not to touch the bottle tip to your eye or other surfaces to avoid potential for eye injury and contamination.

5.2 Uses with Contact Lenses

RESTASIS MULTIDOSE™ 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 MULTIDOSE™** ophthalmic emulsion.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Potential for Eye Injury and Contamination [*see Warnings and Precautions (5.1)*]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In clinical trials, the most common adverse reaction following the use of cyclosporine ophthalmic emulsion, 0.05% was ocular burning (17%).

Other reactions 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).

6.2 Post-marketing Experience

The following adverse reactions have been identified during post approval use of cyclosporine ophthalmic emulsion, 0.05%. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Reported reactions have included: hypersensitivity (including eye swelling, urticaria, rare cases of severe angioedema, face swelling, tongue swelling, pharyngeal edema, and dyspnea); and superficial injury of the eye (from the bottle tip touching the eye during administration).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Clinical administration of cyclosporine ophthalmic emulsion 0.05% is not detected systemically following topical ocular administration [*see Clinical Pharmacology (12.3)*], and maternal use is not expected to result in fetal exposure to the drug. Oral administration of cyclosporine to pregnant rats or rabbits did not produce teratogenicity at clinically relevant doses [*see Data*].

Data

Animal Data

At maternally toxic doses (30 mg/kg/day in rats and 100 mg/kg/day in rabbits), cyclosporine oral solution (USP) was teratogenic as indicated by increased pre- and postnatal mortality, reduced fetal weight and skeletal retardations. These doses (normalized to body surface area) are 5,000 and 32,000 times greater, respectively, than the daily recommended human dose of one drop (approximately 28 mcL) of cyclosporine ophthalmic emulsion 0.05% twice daily 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 during organogenesis

at oral doses up to 17 mg/kg/day or 30 mg/kg/day, respectively. These doses in rats and rabbits are approximately 3,000 and 10,000 times greater, respectively, than the daily recommended human dose.

An oral dose of 45 mg/kg/day cyclosporine administered to rats from Day 15 of pregnancy until Day 21 postpartum produced maternal toxicity and an increase in postnatal mortality in offspring. This dose is 7,000 times greater than the daily recommended human dose. No adverse effects in dams or offspring were observed at oral doses up to 15 mg/kg/day (2,000 times greater than the daily recommended human dose).

8.2 Lactation

Risk Summary

Cyclosporine is known to appear in human milk following systemic administration, but its presence in human milk following topical treatment has not been investigated. Although blood concentrations are undetectable following topical administration of cyclosporine ophthalmic emulsion 0.05% [see *Clinical Pharmacology (12.3)*], caution should be exercised when **RESTASIS MULTIDOSE™** is administered to a nursing woman. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for **RESTASIS MULTIDOSE™** and any potential adverse effects on the breast-fed child from cyclosporine.

8.4 Pediatric Use

Safety and efficacy have not been established in pediatric patients below the age of 16.

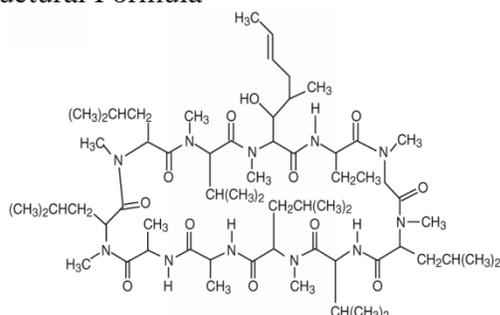
8.5 Geriatric Use

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

11 DESCRIPTION

RESTASIS MULTIDOSE™ (cyclosporine ophthalmic emulsion) 0.05% contains a calcineurin inhibitor immunosuppressant with anti-inflammatory effects. Cyclosporine's chemical name is Cyclo[[*(E)*-(2*S*,3*R*,4*R*)-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 MULTIDOSE™** 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 MULTIDOSE™** ophthalmic emulsion contains: **Active:** cyclosporine 0.05%. **Inactives:** glycerin; castor oil; polysorbate 80; carbomer copolymer type A; purified water; and sodium hydroxide to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 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.

12.3 Pharmacokinetics

Blood cyclosporine 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 cyclosporine ophthalmic emulsion, 0.05%, twice daily, 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 cyclosporine ophthalmic emulsion, 0.05%.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Systemic carcinogenicity studies were conducted 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 80 times greater (normalized to body surface area) than the daily recommended human dose of one drop (approximately 28 mcL) of cyclosporine ophthalmic emulsion, 0.05% twice daily into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed.

Mutagenesis

Cyclosporine has not been found to be 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).

Impairment of Fertility

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 2,000 times the human daily dose of 0.001 mg/kg/day normalized to body surface area) for 9 weeks (male) and 2 weeks (female) prior to mating.

14 CLINICAL STUDIES

Four multicenter, randomized, adequate and well-controlled clinical studies were performed in approximately 1,200 patients with moderate to severe keratoconjunctivitis sicca. Cyclosporine ophthalmic emulsion, 0.05% 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 cyclosporine ophthalmic emulsion, 0.05%-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 cyclosporine ophthalmic emulsion, 0.05%.

16 HOW SUPPLIED/STORAGE AND HANDLING

RESTASIS MULTIDOSE™ ophthalmic emulsion is packaged in a sterile, multi-dose preservative-free bottle. Each bottle consists of a white opaque LDPE bottle, a white opaque polypropylene top with unidirectional valve and air filter, a protective olive green polypropylene cap, and a clear disposable shipping cover over the colored cap.

5.5 mL in 10-mL bottle - NDC 0023-9163-05

Storage: Store at 15-25 °C (59-77 °F).

17 PATIENT COUNSELING INFORMATION

Handling the Container

Advise patients to not allow the tip of the bottle to touch the eye or any surface, as this may contaminate the emulsion. Advise patients to not touch the bottle tip to their eye to avoid the potential for injury to the eye [*see Warnings and Precautions (5.1)*].

Use with Contact Lenses

RESTASIS MULTIDOSE™ should not be administered while wearing contact lenses. Patients with decreased tear production typically should not wear contact lenses. Advise patients that 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 MULTIDOSE™** ophthalmic emulsion [*see Warnings and Precautions (5.2)*].

Administration

Advise patients to read the “Instructions for Use” for detailed first-time use instructions.

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Patented: See: www.allergan.com/products/patents

Made in Ireland.

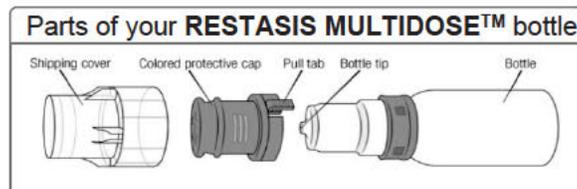


INSTRUCTIONS FOR USE
RESTASIS MULTIDOSE™ (Re stay' sis Mul tee dōs)
(cyclosporine ophthalmic emulsion) 0.05%

Read this Instructions for Use before you start using **RESTASIS MULTIDOSE™** and each time you get a refill. There may be new information. This leaflet does not take the place of talking to your healthcare provider about your medical condition or treatment.

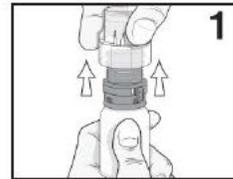
Important:

- **RESTASIS MULTIDOSE™** is for use in the eye
- Wash your hands before using **RESTASIS MULTIDOSE™**.
- Do not let the bottle tip touch the eye or any other surfaces to avoid contamination or injury to your eye.
- Use 1 drop of **RESTASIS MULTIDOSE™** in each eye, 2 times each day, about 12 hours apart.
- If you wear contact lenses, remove them before using **RESTASIS MULTIDOSE™**. Wait for at least 15 minutes before placing them back in your eyes.
- **RESTASIS MULTIDOSE™** can be used with lubricant eye drops, but you should wait at least 15 minutes between using each product.



PREPARING THE BOTTLE FOR FIRST-TIME USE:

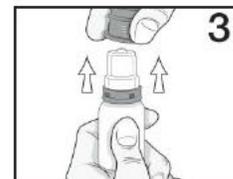
Step 1: Pull off shipping cover by pulling straight up. Throw the shipping cover away. **Do not use RESTASIS MULTIDOSE™** if shipping cover or pull tab are damaged or missing.



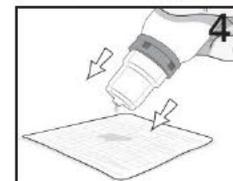
Step 2: Remove the pull tab on the olive green colored protective cap by pulling the end of the pull tab away from the bottle then winding it counterclockwise. Throw away the pull tab.



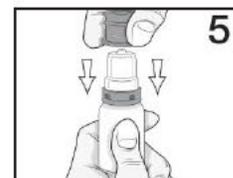
Step 3: Remove the olive green colored protective cap by pulling it straight up. Keep the colored protective cap.



Step 4: Prime the bottle for first time use by squeezing 2 drops onto a tissue. Do not let the bottle tip touch the tissue.



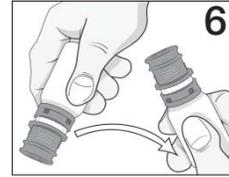
Step 5: The bottle is now ready for use. After use, recap the bottle with the olive green colored protective cap by pushing straight down onto the bottle.



GIVING YOUR DOSE:

Step 6: Turn the bottle upside down a few times before giving your dose to make sure the medicine is mixed well.

Step 7: Instill one drop in the affected eye. Replace the olive green colored protective cap.

**How do I store RESTASIS MULTIDOSE™?**

- Store **RESTASIS MULTIDOSE™** between 15-25 °C (59-77 °F).

Keep RESTASIS MULTIDOSE™ and all medicines out of the reach of children.

This Instructions for Use has been approved by the Food and Drug Administration.

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Approved: 10/2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50790Orig1s25

MEDICAL REVIEW(S)

Medical Officer's Review of NDA 50-790
Prior Approval Supplements

NDA 50-790/S-024/S-025
SDN-1036

Submission Date: September 7, 2016

Receipt Date: September 7, 2016

SDN-1062

Submission Date: October 27, 2016

Receipt Date: October 27, 2016

Review Date: October 27, 2016

Applicant:

Allergan, Inc.
2525 Dupont Drive
Irvine, CA 92612

Applicant's
Representative:

Linda McCauley, Ph.D
Manager, Global Regulatory Affairs
714-246-6217

Drug:

RESTASIS (cyclosporine ophthalmic emulsion) 0.05%

Pharmacologic
Category:

calcineurin inhibitor immunosuppressant

Submitted:

Reference is made to the CMC Prior Approval Supplement (PAS) submitted for NDA 50-790 / S-024 on November 3, 2015. The CMC Supplement provided for a new multi-dose, preservative free presentation of RESTASIS and included labeling specific to the new container closure system. Additional reference is made to the Acknowledgement — Prior Approval Supplement from the Agency dated 29 February 2016 notifying Allergan that the above referenced supplement was split into a CMC S-024 and a Labeling S-025 for administrative reasons. Allergan received Complete Response letters for both Supplements.

Reference is also made to the June 27, 2016, Resubmission of Prior approval CMC Supplement for the new multi-dose, preservative-free presentation of RESTASIS which addresses all of the CMC and Labeling deficiencies in the Complete Response Letter from CMC dated March 2, 2016, and the Complete Response Letter for Labeling dated May 2, 2016.

Reference is also made to the teleconference on August 31, 2016, at which the Division expressed concerns about RESTASIS® (b) (4), the proprietary name under review at the time, and proposed RESTASIS MultiDose. The applicant has now submitted an Amendment to the Prior Approval CMC Supplement with revised labeling reflecting the new proposed proprietary name, RESTASIS MultiDose™.

Chemistry Manufacturing Review #2 of S-024 (dated 10/14/16)

See CMC review #1 in DARRTS dated 2/29/16 for additional background. All the CMC aspects of this supplemental application (S-024) were found acceptable in review #1. However, the microbiology review raised deficiencies that needed to be resolved prior to approval of this supplement. A Complete Response Letter (CR) dated March 2, 2016, containing all the microbiology deficiencies was sent to the applicant.

The applicant responded to all the deficiencies in the submission dated June 27, 2016. Review of these responses by the Agency, generated a second Information Request (IR), which was sent to the applicant on September 2, 2016. The applicant responded to this IR in the submission dated September 14, 2016.

Review of all the responses to the microbiology deficiencies was conducted by Dr. Yarery Smith from the microbiology review team. Dr. Smith found all the responses acceptable on October 11, 2016.

All CMC outstanding issues in this supplement have been satisfactorily resolved. From the point of view of CMC, this supplement is recommended for approval.

Product Quality Microbiology Review #2 of S-024 (dated 10/11/16)

See Product Quality Microbiology review #1 in Panorama dated 2/25/16 for additional background. The supplement (S-024) is now recommended for approval on the basis of sterility assurance.

The outstanding microbiological issues related to this supplemental application and noted in the Complete Response Letter (CR) dated March 2, 2016, have been adequately addressed.

Division of Medication Error Prevention and Analysis (DMEPA) Review of S-025

DMEPA completed a review of the submitted labeling on 10/24/16.

DMEPA Prescribing Information – Section 2.1 Preparation for First-Time Use and Section 2.2 Preparation for Use

1. We note that the instructions refer to the “colored protective cap”. Consider revising the images from black and white to color to improve clarity and maintain consistency with the carton labeling.

DTOP: Disagree. The shipping cap is opaque. Only the protective cap is colored. We would not recommend that the applicant print their package insert/Instructions for Use in color to show a colored cap. We would recommend Section 2.1 and 2.2, the description (Section 16), and the Instructions for Use state that the protective cap is olive green.

2. As this product will be used by laypersons, consider removing the instructions for use (Section 2.1 and 2.2) from Section 2 Dosage and Administration, and refer to the Instructions for Use located at the end of the Prescribing Information.

DTOP: Disagree. The Patient Instructions for Use should not contain information not found in the package insert. Revision of Section 2.1 and 2.2 to remove these instructions is not recommended.

A. Container Label and Carton Labeling

1. Increase the size of the established name and strength to improve readability of this important information.

DTOP: Agree. The company will be told that the established name should be a font size that is at least half as large of that of the proprietary name and a prominence commensurate with the proprietary name, as stated in 21 CFR 201.10(g)(2).

B. Carton Labeling

1. Add the statement [REDACTED] (b) (4) on the side panel to maintain consistency with the prescribing information. In addition include a place for patients to [REDACTED] (b) (4)

DTOP: Disagree. The references to [REDACTED] (b) (4) will be removed from the package insert, Sections 16 and 17. They are not supported by the application.

3. Include the term “Multiple Dose” to improve clarity and ensure that the product is safely used and handled.

DTOP: Disagree. Patients may choose to use the product once then discard. The name of the product, Restasis Multidose, and the instructions provided are adequate to relate that this is a multiple dose product.

3. Ensure the Instructions for Use (IFU) provided on the carton are consistent with the IFU in the Prescribing Information regarding preparing the bottle for first time use and giving the dose.

DTOP: The IFU on the carton is not contradictory with the full IFU. The IFU on the carton does not have enough space to include the full IFU and cannot be as detailed as the separate IFU.

Division of Medical Policy Programs (DMPP) and Office of Prescription Drug Promotion (OPDP) Revoew of S-025

DMPP and OPDP completed a review of the submitted Instructions for Use labeling on 10/24/16. DTOP had minor additional revisions to the DMPP /OPDP labeling. In an email exchange dated 10/25/16, DMPP /OPDP had no objection to DTOP’s additional revisions to the Instructions for Use.

Following is the applicant’s proposed draft labeling (S-025) for RESTASIS MultiDose™ submitted 10/26/16.

12 Page(s) have been Withheld in Full as draft labeling, b4 (CCI/TS) immediately following this page

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/s/

RHEA A LLOYD
10/27/2016

WILEY A CHAMBERS
10/27/2016

Medical Officer's Review of NDA 50-790
Prior Approval Labeling Supplement

NDA 50-790/S-024
SDN-913

Submission Date: November 3, 2015
Receipt Date: November 3, 2015
Review Date: February 18, 2016

Applicant:

Allergan, Inc.
2525 Dupont Drive
Irvine, CA 92612

Applicant's
Representative:

Kathrin Schalper, Ph.D., RAC, PMP
Senior Manager, Global Regulatory Affairs
714-246-4188

Drug:

RESTASIS (cyclosporine ophthalmic
emulsion) 0.05%

Pharmacologic
Category:

topical immunomodulator

Submitted:

The applicant has submitted a Prior Approval CMC Supplement for the addition of a Multi-Dose
(b) (4) Container Closure for RESTASIS, in addition to the existing unit-
dose vial presentation. The composition and strength of cyclosporine ophthalmic emulsion
0.05% supplied in the new container closure system is unchanged. The submission also includes
a Request for Proprietary Name Review for the proposed Proprietary Name "RESTASIS
(b) (4),,

The CMC portion of Supplement 24 for the Multi-Dose Preservative-Free Container Closure
system, received a Complete Response on March 2, 2016.

Following is the applicant's proposed labeling for RESTASIS (b) (4)

Reviewer proposed additions are noted by underline and deletions by s .

Acting Associate Director of Labeling additions are noted by underline and deletions by within
the review.

Reviewers' Comments:

The CMC supplement for the Multi-Dose Preservative-Free Container Closure system, received a Complete Response on March 2, 2016. Additionally, the proposed proprietary name “RESTASIS [REDACTED]”^{(b) (4)} is not acceptable because it may be misleading. The proposed modifier to the current trade name may imply that new technology or improvements have been made to the drug product in addition to the change packaging configuration. The drug product in the proposed new packaging configuration is the same as that in the current packaging configuration.

All reference to the new container closure system and the new trade name has been struck throughout the labeling. The currently approved language in the RESTASIS carton and container labeling should be retained.

Recommendations:

This supplement is not recommended for approval with the current labeling. Product labeling consistent with the revisions within this review should be submitted.

Rhea A. Lloyd, M.D.
Medical Officer

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/s/

RHEA A LLOYD
04/27/2016

WILLIAM M BOYD
04/27/2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50790Orig1s25

PHARMACOLOGY REVIEW(S)

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number: 50790
Supporting document/s: SDN913
Applicant's letter date: 11-03-2015
CDER stamp date: 11-03-2015
Product: Restasis® (Cyclosporine Ophthalmic Emulsion,
0.05%)
Indication: To increase tear production in patients whose
tear production is presumed to be suppressed
due to ocular inflammation associated with
keratoconjunctivitis sicca.
Applicant: Allergan
2525 Dupont Drive MC and 150B
Irvine, CA 92623
Review Division: Division of Transplant and Ophthalmology
Products
Reviewer: Aaron Ruhland, PhD
Supervisor/Team Leader: Lori Kotch, PhD, DABT
Division Director: Renata Albrecht, MD
Project Manager: Jacquelyn Smith

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 50790 are owned by Allergan or are data for which Allergan has obtained a written right of reference.

Any information or data necessary for approval of NDA 50790 that Allergan does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 50790.

1 Executive Summary

1.1 Introduction

In this submission, the applicant has proposed a new packaging container (CMC supplement), termed [REDACTED] ^{(b) (4)}, as well as changes to the current product labeling which include the conversion of Section 8 to PLLR format and changes to Section 13.

1.3.3 Labeling

1.3.3.1 Current Labeling (updated 12/03/2012; reviewed by Lori Kotch PhD, DABT dated 10-10-2012)

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C

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 5,000 and 32,000 times greater (normalized to body surface area), respectively, than the daily human dose of one drop (approximately 28 mL) of 0.05% RESTASIS® twice daily 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 3,000 and 10,000 times greater (normalized to body surface area), 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 postpartum, a maternally toxic level, exhibited an increase in postnatal mortality; this dose is 7,000 times greater than the daily human topical dose (0.001 mg/kg/day) normalized to body surface area assuming that the entire dose is absorbed. No adverse events were observed at oral doses up to 15 mg/kg/day (2,000 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 a pregnant woman only if clearly needed.

8.3 Nursing Mothers

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

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: 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 80 times greater (normalized to body surface area) than the daily human dose of one drop (approximately 28 mcL) of 0.05% RESTASIS® twice daily into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed.

Mutagenesis: Cyclosporine has not been found to be 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).

Impairment of Fertility: 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 2,000 times the human daily dose of 0.001 mg/kg/day normalized to body surface area) for 9 weeks (male) and 2 weeks (female) prior to mating.

1.3.3.2 Applicant's Proposed Labeling

8.1 Pregnancy

Risk Summary

Clinical administration of cyclosporine ophthalmic emulsion 0.05% is not (b) (4) systemically following topical ocular administration, and maternal use is not expected to result in fetal exposure to the drug. (b) (4)

(b) (4)

(b) (4)

(b) (4)

Data

Animal Data

(b) (4)

8.2 Lactation

Risk Summary

Cyclosporine is known to appear in human milk following systemic administration, but presence in human milk after topical treatment has not been investigated. Although blood concentrations are undetectable after topical administration of cyclosporine ophthalmic emulsion 0.05%, caution should be exercised when RESTASIS (b) (4)™ is administered to a nursing woman.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: 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 (b) (4) 80 times greater (normalized

to body surface area), respectively, than the daily human dose of one drop (approximately 28 mcL) of cyclosporine ophthalmic emulsion 0.05% twice daily into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed.

Mutagenesis: Cyclosporine has not been found to be 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).

Impairment of Fertility: 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 2,000 times the human daily dose of 0.001 mg/kg/day normalized to body surface area) for 9 weeks (male) and 2 weeks (female) prior to mating.

1.3.3.3 FDA's Changes to Applicant's Proposed Labeling

For the proposed changes to sections 8 and 13, the applicant has calculated human dose to be (b) (4) mg/kg/day for 60 kg adult or (b) (4), based on bilateral administration of Restasis at the recommended human dose (RHD). Regarding changes to Section 8 and PLLR reformatting, the content proposed by the while acceptable in content requires additional details and formatting based on PLLR guidance.

For the proposed changes to Section 13, the applicant has included the addition of a safety margin of (b) (4) fold for comparison of the human dose and the low dose in the mouse (b) (4). The safety margin of (b) (4) cannot be replicated by this reviewer and the current labeling which reports the safety margin as approximately 80-fold appears to remain accurate. Therefore, the following content should be recommended for the updated labeling:

8.1 Pregnancy

Risk Summary

Clinical administration of cyclosporine ophthalmic emulsion 0.05% is not detected systemically following topical ocular administration [see *Clinical Pharmacology (12.3)*], and maternal use is not expected to result in measurable fetal exposure to the drug. Oral administration of cyclosporine to pregnant rats or rabbits did not produce teratogenicity at clinically relevant doses.

Data

Animal Data

At maternally toxic doses (30 mg/kg/day in rats and 100 mg/kg/day in rabbits), cyclosporine oral solution (USP) was teratogenic, as indicated by increased pre- and postnatal mortality, reduced fetal weight and skeletal retardations. These doses (normalized to body surface area) are 5,000 and 32,000 times greater, respectively, than the daily recommended human dose of one drop (approximately 28 mcL) of cyclosporine ophthalmic emulsion 0.05% RESTASIS® twice daily into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed. No evidence of embryo-fetal toxicity was observed in rats or rabbits receiving cyclosporine during organogenesis at oral doses up to 17 mg/kg/day or 30 mg/kg/day, respectively. These doses in rats and rabbits are approximately 3,000 and 10,000 times greater, respectively, than the daily recommended human dose.

An oral dose of 45 mg/kg/day cyclosporine administered to rats from Day 15 of pregnancy until Day 21 postpartum produced maternal toxicity and an increase in postnatal mortality in offspring. This dose is 7,000 times greater than the daily recommended human dose. No adverse effects in dams or offspring were observed at oral doses up to 15 mg/kg/day (2,000 times greater than the daily recommended human dose).

8.2 Lactation

Risk Summary

Cyclosporine is known to appear in human milk following systemic administration, but its presence in human milk following topical treatment has not been investigated. Although blood concentrations are undetectable following topical administration of cyclosporine ophthalmic emulsion 0.05% [see *Clinical Pharmacology (12.3)*], caution should be exercised when (b) (4) is administered to a nursing woman. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for (b) (4) and any potential adverse effects on the breast-fed child from cyclosporine (b) (4).

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Systemic carcinogenicity studies were conducted 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 80 times greater (normalized to body surface area), (b) (4), than the daily recommended human dose of one drop (approximately 28 mcL) of 0.05% RESTASIS twice daily into each eye of a 60 kg person (0.001 mg/kg/day), assuming that the entire dose is absorbed.

Mutagenesis: Cyclosporine has not been found to be 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).

Impairment of Fertility: 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 2,000 times the human daily dose of 0.001 mg/kg/day, normalized to body surface area) for 9 weeks (male) and 2 weeks (female) prior to mating.

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/s/

AARON M RUHLAND
04/21/2016

LORI E KOTCH
04/21/2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50790Orig1s25

OTHER REVIEW(S)

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: October 24, 2016

To: Jacquelyn Smith
Regulatory Project Manager
Division of Transplant and Ophthalmology Products (DTOP)

From: Carrie Newcomer, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: **NDA: 050790**
RESTASIS MULTIDOSE™ (cyclosporine ophthalmic emulsion)
0.05%

On October 17, 2016, DTOP consulted OPDP to review the proposed package insert (PI) for RESTASIS MULTIDOSE™ (cyclosporine ophthalmic emulsion) 0.05%.

OPDP has reviewed the proposed PI and our comments are based on the substantially complete version of the draft label that was attached to the October 17, 2016 consult request from DTOP.

OPDP does not have any comments on the draft PI, attached.

The Division of Medical Policy Programs (DMPP) and OPDP will provide comments on the IFU in a joint review under separate cover.

Thank you for your consult. If you have any questions on the PI, please contact Carrie Newcomer at 6-1233, or carrie.newcomer@fda.hhs.gov.

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/s/

CARRIE A NEWCOMER
10/24/2016

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: October 24, 2016

To: Renata Albrecht, MD
Director
Division of Transplant and Ophthalmology Products (DTOP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Shawna Hutchins, MPH, BSN, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon W. Williams, MSN, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Carrie Newcomer, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Instructions for Use (IFU)

Drug Name (established name): RESTASIS MULTIDOSE (cyclosporine ophthalmic) 0.05%

Dosage Form and Route: for topical ophthalmic use

Application Type/Number: NDA 50790

Supplement Number: S-025

Applicant: Allergen Inc.

1 INTRODUCTION

On November 3, 2015, Allergen Inc, submitted for the Agency's review a Chemical Manufacturing, Control (CMS) Prior Approval Supplement (PAS) for NDA 50-790/S-024. The CMC PAS provided for a new multi-dose, preservative free presentation of RESTASIS and included labeling specific to a new container closure system. On February 29, 2016 the Agency notified the Applicant that the supplement was split into a CMC PAS S-024 and a Labeling PAS S-025 for administrative reasons. Allergen received Complete Response letters for both supplements. On June 27, 2016, the Applicant addressed all CMC and labeling deficiencies and included them in the CMC Prior Approval Supplement-Resubmission.

The purpose of this submission is to seek approval for RESTASIS (cyclosporine ophthalmic emulsion) 0.05%, for topical ophthalmic use, indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Transplant and Ophthalmology Products (DTOP) on October 11, 2016 for DMPP and on October 17, 2016 for OPDP to review the Applicant's proposed Instructions for Use (IFU) for RESTASIS (cyclosporine ophthalmic emulsion) 0.05%, for topical ophthalmic use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

2 MATERIAL REVIEWED

- Draft RESTASIS (cyclosporine ophthalmic emulsion) 0.05%, for topical ophthalmic use IFU received on June 27, 2016, and received by DMPP on October 11, 2016.
- Draft RESTASIS (cyclosporine ophthalmic emulsion) 0.05%, for topical ophthalmic use IFU received on June 27, 2016, and received by OPDP on October 17, 2016.
- Draft RESTASIS (cyclosporine ophthalmic emulsion) 0.05%, for topical ophthalmic Prescribing Information (PI) received on June 27, 2016 revised by the Review Division throughout the review cycle, and received by DMPP on October 11, 2016.
- Draft RESTASIS (cyclosporine ophthalmic emulsion) 0.05%, for topical ophthalmic Prescribing Information (PI) received on June 27, 2016 revised by the Review Division throughout the review cycle, and received by OPDP on October 17, 2016.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the IFU using the Arial font, size 10.

In our collaborative review of the IFU we:

- simplified wording and clarified concepts where possible
- ensured that the IFU is consistent with the Prescribing Information (PI)
- ensured that the IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the IFU.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
10/24/2016

CARRIE A NEWCOMER
10/24/2016

SHAWNA L HUTCHINS
10/24/2016

LASHAWN M GRIFFITHS
10/24/2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50790Orig1s25

PROPRIETARY NAME REVIEW(S)

PROPRIETARY NAME REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	October 20, 2016
Application Type and Number:	NDA 050790
Product Name and Strength:	Restasis MultiDose (Cyclosporine Ophthalmic Emulsion) 0.05%
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Allergan
Panorama #:	2016-10068753
DMEPA Primary Reviewer:	Lissa C. Owens, PharmD
DMEPA Team Leader:	Mishale Mistry, PharmD, MPH
DMEPA Deputy Director:	Lubna Merchant, PharmD, MS

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1 INTRODUCTION

This review evaluates the proposed proprietary name, Restasis MultiDose, from a safety and misbranding perspective. The sources and methods used to evaluate the proposed name are outlined in the reference section and Appendix A respectively. The Applicant did not submit an external name study for this proposed proprietary name.

1.1 REGULATORY HISTORY

The Applicant previously submitted the proposed proprietary name, Restasis (b)(4)*** on April 2, 2015. However, the Division of Medication Error Prevention and Analysis (DMEPA) found the name, Restasis (b)(4)*** unacceptable due to misbranding concerns in OSE Review #2015-81036, dated July 21, 2015.

Subsequently, the Applicant submitted the name, Restasis (b)(4)***, for review on November 3, 2015 but the application received a Complete Response (CR) on March 2, 2016.

On June 27, 2016, the Applicant submitted Restasis (b)(4)*** for our review. The Division of Transplant and Ophthalmic Products (DTOP) noted some concerns with the modifier '(b)(4)', and a teleconference was held on August 31, 2016 to inform the Applicant of these concerns^a.

Thus, the Applicant withdrew the name Restasis (b)(4)*** on September 1, 2016 and submitted the name, Restasis MultiDose, for review on September 7, 2016.

1.2 PRODUCT INFORMATION

The following product information is provided in the September 7, 2016 proprietary name submission.

- Intended Pronunciation: Re stay' sis Mul tee dōs
- Active Ingredient: Cyclosporine
- Indication of Use: To increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with keratoconjunctivitis sicca.
- Route of Administration: Ophthalmic
- Dosage Form: Ophthalmic Emulsion
- Strength: 0.05%
- Dose and Frequency: 1 drop into each eye twice daily approximately 12 hours apart
- How Supplied: Sterile, multi-dose preservative-free white opaque LDPE bottle
- Storage: (b)(4)
(b)(4)

^a Higgins, J. Memorandum of Teleconference for Restasis (b)(4) (NDA 050790) Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology 2016 Sep 14.

2 RESULTS

The following sections provide information obtained and considered in the overall evaluation of the proposed proprietary name.

2.1 MISBRANDING ASSESSMENT

The Office of Prescription Drug Promotion (OPDP) determined that the proposed name would not misbrand the proposed product. DMEPA and the Division of Transplant and Ophthalmic Products (DTOP) concurred with the findings of OPDP's assessment of the proposed name.

2.2 SAFETY ASSESSMENT

The following aspects were considered in the safety evaluation of the name.

2.2.1 *United States Adopted Names (USAN) Search*

There is no USAN stem present in the proprietary name or modifier^b.

2.2.2 *Components of the Proposed Proprietary Name*

The proprietary name consists of a root name and a modifier. The Applicant indicated in their submission that the proposed root name, Restasis, is the root proprietary name of the existing product line. In order to distinguish the existing single dose, preservative free bottle from the new multi-dose, preservative free bottle, Allergan proposes to add MultiDose as a modifier after the existing root proprietary name RESTASIS®, resulting in RESTASIS MultiDose™. This product will be added to the existing “Restasis” product line that is comprised of single-dose bottle. Therefore, we have evaluated whether or not the proposed name requires the modifier, and evaluated the appropriateness of the chosen modifier ‘MultiDose.’ Our evaluation is discussed in Section 2.2.4.

2.2.3 *FDA Name Simulation Studies*

Fifty-five practitioners participated in DMEPA's prescription studies. The responses did overlap with the currently marketed product ‘Restasis’ as the name is the proposed root name. In addition, six (outpatient n= 2, voice n=1, inpatient n=3) participants in the prescription study listed ‘Restasis’ without the modifier, ‘MultiDose’. We discuss the omission of the modifier in Section 2.2.4. The responses did not sound or look similar to any currently marketed products or any products in the pipeline. Appendix B contains the results from the verbal and written prescription studies.

2.2.4 *Safety assessment of the modifier*

The root name, ‘Restasis’ is currently approved as single-use LDPE vials, and has been on the market since December 2002. We have not received any medication errors related to name confusion with Restasis. The currently marketed product and the proposed product are both

^b USAN stem search conducted on September 7, 2016

cyclosporine and differ in that the proposed product is a multiple dose bottle. Therefore, we agree with the use of the same root name “Restasis” for the proposed product.

The addition of a modifier to ‘Restasis’ will further differentiate the product from the current single-dose LDPE vials. It is not uncommon for modifiers to be used to denote a specific formulation or packaging configuration as part of a product line extension. In the case of Restasis MultiDose, the modifier ‘MultiDose’ is intended to distinguish this product from the existing single dose product.

However, we also note that omission and oversight of modifiers is cited in literature as a common cause of medication error and was seen in the prescription study.^c Postmarket experience shows that the introduction of product line extensions result in medication errors if the modifier is omitted and the product characteristics are similar or overlap. We considered the potential safety implications of this error and note that the patient will still receive the correct drug product however, in a different packaging configuration.

2.2.5 Based on the totality of information considered above, we find the use of the proposed modifier, “Multidose”, acceptable for this product. Medication Error Data Selection of Cases

We searched the FDA Adverse Event Reporting System (FAERS) database using the strategy listed in Table 2 (see Appendix A1 for a description of FAERS database) for name confusion errors involving *Restasis MultiDose* that would be relevant for this review.

Table 2. FAERS Search Strategy	
Search Date	October 4, 2016
Drug Name	Restasis
Event (MedDRA Terms)	<p>DMEPA Official PNR Name Confusion Search Terms Event List:</p> <p>Preferred Terms: CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR (DRUG ADMINISTRATION ERROR) DRUG DISPENSING ERROR DRUG PRESCRIBING ERROR INTERCEPTED DRUG DISPENSING ERROR INTERCEPTED DRUG PRESCRIBING ERROR INTERCEPTED MEDICATION ERROR MEDICATION ERROR PRODUCT NAME CONFUSION TRANSCRIPTION MEDICATION ERROR</p> <p>Lower Level Terms: INTERCEPTED PRODUCT SELECTION ERROR</p>

^c Lesar TS. Prescribing Errors Involving Medication Dosage Forms. J Gen Intern Med. 2002; 17(8): 579-587

	INTERCEPTED WRONG DRUG PRODUCT SELECTED INTERCEPTED WRONG DRUG SELECTED PRODUCT SELECTION ERROR WRONG DEVICE DISPENSED WRONG DRUG ADMINISTERED WRONG DRUG DISPENSED WRONG DRUG PRESCRIBED WRONG DRUG PRODUCT SELECTED WRONG DRUG SELECTED WRONG PRODUCT SELECTED
Date Limits	No date limitation

Each report was reviewed for relevancy and duplication. Duplicates were merged into a single case. The NCC MERP Taxonomy of Medication Errors was used to code the case outcome and error root causes when provided by the reporter.

After individual review, there were no reports included in the final analysis as they did not describe confusion with the root name, Restasis.

3 CONCLUSIONS

The proposed proprietary name is acceptable.

If you have any questions or need clarifications, please contact Janet Higgins, OSE project manager, at 240-402-0330.

3.1 COMMENTS TO THE APPLICANT

We have completed our review of the proposed proprietary name, Restasis MultiDose, and have concluded that this name is acceptable.

If any of the proposed product characteristics as stated in your September 7, 2016 submission are altered prior to approval of the marketing application, the name must be resubmitted for review.

4 REFERENCES

1. *USAN Stems* (<http://www.ama-assn.org/ama/pub/physician-resources/medical-science/united-states-adopted-names-council/naming-guidelines/approved-stems.page>)

USAN Stems List contains all the recognized USAN stems.

2. *Phonetic and Orthographic Computer Analysis (POCA)*

POCA is a system that FDA designed. As part of the name similarity assessment, POCA is used to evaluate proposed names via a phonetic and orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists that operates in a similar fashion. POCA is publicly accessible.

Drugs@FDA

Drugs@FDA is an FDA Web site that contains most of the drug products approved in the United States since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA-approved *brand name* and *generic drugs*; *therapeutic biological products*, *prescription* and *over-the-counter* human drugs; and *discontinued drugs* (see Drugs @ FDA Glossary of Terms, available at <http://www.fda.gov/Drugs/InformationOnDrugs/ucm079436.htm#ther biological>).

RxNorm

RxNorm contains the names of prescription and many OTC drugs available in the United States. RxNorm includes generic and branded:

- Clinical drugs – pharmaceutical products given to (or taken by) a patient with therapeutic or diagnostic intent
- Drug packs – packs that contain multiple drugs, or drugs designed to be administered in a specified sequence

Radiopharmaceuticals, contrast media, food, dietary supplements, and medical devices, such as bandages and crutches, are all out of scope for RxNorm (<http://www.nlm.nih.gov/research/umls/rxnorm/overview.html#>).

Division of Medication Errors Prevention and Analysis proprietary name consultation requests

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

3. *Electronic Drug Registration and Listing System (eDRLS) database*

The electronic Drug Registration and Listing System (eDRLS) was established to support the FDA's Center for Drug Evaluation and Research (CDER) goal to establish a common Structured Product Labeling (SPL) repository for all facilities that manufacture regulated drugs. The system is a reliable, up-to-date inventory of FDA-regulated, drugs and establishments that produce drugs and their associated information.

APPENDICES

Appendix A

FDA's Proprietary Name Risk Assessment evaluates proposed proprietary names for misbranding and safety concerns.

1. **Misbranding Assessment:** For prescription drug products, OPDP assesses the name for misbranding concerns. . For over-the-counter (OTC) drug products, the misbranding assessment of the proposed name is conducted by DNDP. OPDP or DNDP evaluates proposed proprietary names to determine if the name is false or misleading, such as by making misrepresentations with respect to safety or efficacy. For example, a fanciful proprietary name may misbrand a product by suggesting that it has some unique effectiveness or composition when it does not (21 CFR 201.10(c)(3)). OPDP or DNDP provides their opinion to DMEPA for consideration in the overall acceptability of the proposed proprietary name.
2. **Safety Assessment:** The safety assessment is conducted by DMEPA, and includes the following:
 - a. **Preliminary Assessment:** We consider inclusion of USAN stems or other characteristics that when incorporated into a proprietary name may cause or contribute to medication errors (i.e., dosing interval, dosage form/route of administration, medical or product name abbreviations, names that include or suggest the composition of the drug product, etc.) See prescreening checklist below in Table 2*. DMEPA defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.^d

^d National Coordinating Council for Medication Error Reporting and Prevention.
<http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

***Table 2- Prescreening Checklist for Proposed Proprietary Name**

	Answer the questions in the checklist below. Affirmative answers to any of these questions indicate a potential area of concern that should be carefully evaluated as described in this guidance.
Y/N	Is the proposed name obviously similar in spelling and pronunciation to other names?
	Proprietary names should not be similar in spelling or pronunciation to proprietary names, established names, or ingredients of other products.
Y/N	Are there medical and/or coined abbreviations in the proprietary name?
	Proprietary names should not incorporate medical abbreviations (e.g., QD, BID, or others commonly used for prescription communication) or coined abbreviations that have no established meaning.
Y/N	Are there inert or inactive ingredients referenced in the proprietary name?
	Proprietary names should not incorporate any reference to an inert or inactive ingredient in a way that might create an impression that the ingredient's value is greater than its true functional role in the formulation (21 CFR 201.10(c)(4)).
Y/N	Does the proprietary name include combinations of active ingredients?
	Proprietary names of fixed combination drug products should not include or suggest the name of one or more, but not all, of its active ingredients (see 21 CFR 201.6(b)).
Y/N	Is there a United States Adopted Name (USAN) stem in the proprietary name?
	Proprietary names should not incorporate a USAN stem in the position that USAN designates for the stem.
Y/N	Is this proprietary name used for another product that does not share at least one common active ingredient?
	Drug products that do not contain at least one common active ingredient should not use the same (root) proprietary name.
Y/N	Is this a proprietary name of a discontinued product?
	Proprietary names should not use the proprietary name of a discontinued product if that discontinued drug product does not contain the same active ingredients.

- b. Phonetic and Orthographic Computer Analysis (POCA): Following the preliminary screening of the proposed proprietary name, DMEPA staff evaluates the proposed name against potentially similar names. In order to identify names with potential similarity to the proposed proprietary name, DMEPA enters the proposed proprietary name in POCA and queries the name against the following drug reference databases, Drugs@fda, CernerRxNorm, and names in the review pipeline using a 50% threshold in POCA. DMEPA reviews the combined orthographic and phonetic matches and group the names into one of the following three categories:
- Highly similar pair: combined match percentage score $\geq 70\%$.
 - Moderately similar pair: combined match percentage score $\geq 50\%$ to $\leq 69\%$.
 - Low similarity: combined match percentage score $\leq 49\%$.

Using the criteria outlined in the check list (Table 3-5) that corresponds to each of the three categories (highly similar pair, moderately similar pair, and low similarity), DMEPA evaluates the name pairs to determine the acceptability or non-acceptability of a proposed proprietary name. The intent of these checklists is to increase the transparency and predictability of the safety determination of whether a proposed name is vulnerable to confusion from a look-alike or sound-alike perspective. Each bullet below corresponds to the name similarity category cross-references the respective table that addresses criteria that DMEPA uses to determine whether a name presents a safety concern from a look-alike or sound-alike perspective.

- For highly similar names, differences in product characteristics often cannot mitigate the risk of a medication error, including product differences such as strength and dose. Thus, proposed proprietary names that have a combined score of ≥ 70 percent are at risk for a look-alike sound-alike confusion which is an area of concern (See Table 3).
- Moderately similar names with overlapping or similar strengths or doses represent an area for concern for FDA. The dosage and strength information is often located in close proximity to the drug name itself on prescriptions and medication orders, and it can be an important factor that either increases or decreases the potential for confusion between similarly named drug pairs. The ability of other product characteristics to mitigate confusion (e.g., route, frequency, dosage form, etc.) may be limited when the strength or dose overlaps. We review such names further, to determine whether sufficient differences exist to prevent confusion. (See Table 4).
- Names with low similarity that have no overlap or similarity in strength and dose are generally acceptable (See Table 5) unless there are data to suggest that the name might be vulnerable to confusion (e.g., prescription simulation study suggests that the name is likely to be misinterpreted as a marketed product). In these instances, we would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

- c. FDA Prescription Simulation Studies: DMEPA staff also conducts a prescription simulation studies using FDA health care professionals.

Three separate studies are conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of the proposed proprietary name with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. The studies employ healthcare professionals (pharmacists, physicians, and nurses), and attempts to simulate the prescription ordering process. The primary Safety Evaluator uses the results to identify orthographic or phonetic vulnerability of the proposed name to be misinterpreted by healthcare practitioners.

In order to evaluate the potential for misinterpretation of the proposed proprietary name in handwriting and verbal communication of the name, inpatient medication orders and/or outpatient prescriptions are written, each consisting of a combination of marketed and unapproved drug products, including the proposed name. These orders are optically scanned and one prescription is delivered to a random sample of participating health professionals via e-mail. In addition, a verbal prescription is recorded on voice mail. The voice mail messages are then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants record their interpretations of the orders which are recorded electronically.

- d. Comments from Other Review Disciplines: DMEPA requests the Office of New Drugs (OND) and/or Office of Generic Drugs (OGD), ONDQA or OBP for their comments or concerns with the proposed proprietary name, ask for any clinical issues that may impact the DMEPA review during the initial phase of the name review. Additionally, when applicable, at the same time DMEPA requests concurrence/non-concurrence with OPDP's decision on the name. The primary Safety Evaluator addresses any comments or concerns in the safety evaluator's assessment.

The OND/OGD Regulatory Division is contacted a second time following our analysis of the proposed proprietary name. At this point, DMEPA conveys their decision to accept or reject the name. The OND or OGD Regulatory Division is requested to provide any further information that might inform DMEPA's final decision on the proposed name.

Additionally, other review disciplines opinions such as ONDQA or OBP may be considered depending on the proposed proprietary name.

When provided, DMEPA considers external proprietary name studies conducted by or for the Applicant/Sponsor and incorporates the findings of these studies into the overall risk assessment.

The DMEPA primary reviewer assigned to evaluate the proposed proprietary name is responsible for considering the collective findings, and provides an overall risk assessment of the proposed proprietary name.

Table 3. Highly Similar Name Pair Checklist (i.e., combined Orthographic and Phonetic score is \geq 70%).

Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may render the names less likely to confusion, provided that the pair does not share a
--

common strength or dose.			
<u>Orthographic Checklist</u>		<u>Phonetic Checklist</u>	
Y/N	Do the names begin with different first letters? <i>Note that even when names begin with different first letters, certain letters may be confused with each other when scripted.</i>	Y/N	Do the names have different number of syllables?
Y/N	Are the lengths of the names dissimilar* when scripted? <i>*FDA considers the length of names different if the names differ by two or more letters.</i>	Y/N	Do the names have different syllabic stresses?
Y/N	Considering variations in scripting of some letters (such as z and f), is there a different number or placement of upstroke/downstroke letters present in the names?	Y/N	Do the syllables have different phonologic processes, such vowel reduction, assimilation, or deletion?
Y/N	Is there different number or placement of cross-stroke or dotted letters present in the names?	Y/N	Across a range of dialects, are the names consistently pronounced differently?
Y/N	Do the infixes of the name appear dissimilar when scripted?		
Y/N	Do the suffixes of the names appear dissimilar when scripted?		

Table 4: Moderately Similar Name Pair Checklist (i.e., combined score is $\geq 50\%$ to $\leq 69\%$).

Step 1	Review the DOSAGE AND ADMINISTRATION and HOW SUPPLIED/STORAGE AND HANDLING sections of the prescribing information (or for OTC drugs refer to the Drug Facts label) to determine if strengths and doses of the name pair overlap or are very similar. Different strengths and doses for products whose names are moderately similar may decrease the risk of confusion between the moderately similar name pairs. Name
--------	--

	<p>pairs that have overlapping or similar strengths or doses have a higher potential for confusion and should be evaluated further (see Step 2). Because the strength or dose could be used to express an order or prescription for a particular drug product, overlap in one or both of these components would be reason for further evaluation.</p> <p>For single strength products, also consider circumstances where the strength may not be expressed.</p> <p>For any i.e. drug products comprised of more than one active ingredient, consider whether the strength or dose may be expressed using only one of the components.</p> <p>To determine whether the strengths or doses are similar to your proposed product, consider the following list of factors that may increase confusion:</p> <ul style="list-style-type: none"> • Alternative expressions of dose: 5 mL may be listed in the prescribing information, but the dose may be expressed in metric weight (e.g., 500 mg) or in non-metric units (e.g., 1 tsp, 1 tablet/capsule). Similarly, a strength or dose of 1000 mg may be expressed, in practice, as 1 g, or vice versa. • Trailing or deleting zeros: 10 mg is similar in appearance to 100 mg which may potentiate confusion between a name pair with moderate similarity. • Similar sounding doses: 15 mg is similar in sound to 50 mg
Step 2	<p>Answer the questions in the checklist below. Affirmative answers to some of these questions suggest that the pattern of orthographic or phonetic differences in the names may reduce the likelihood of confusion for moderately similar names <u>with</u> overlapping or similar strengths or doses.</p>

	<p>Orthographic Checklist (Y/N to each question)</p> <ul style="list-style-type: none"> Do the names begin with different first letters? Note that even when names begin with different first letters, certain letters may be confused with each other when scripted. Are the lengths of the names dissimilar* when scripted? *FDA considers the length of names different if the names differ by two or more letters. Considering variations in scripting of some letters (such as <i>z</i> and <i>f</i>), is there a different number or placement of upstroke/downstroke letters present in the names? Is there different number or placement of cross-stroke or dotted letters present in the names? Do the infixes of the name appear dissimilar when scripted? Do the suffixes of the names appear dissimilar when scripted? 	<p>Phonetic Checklist (Y/N to each question)</p> <ul style="list-style-type: none"> Do the names have different number of syllables? Do the names have different syllabic stresses? Do the syllables have different phonologic processes, such as vowel reduction, assimilation, or deletion? Across a range of dialects, are the names consistently pronounced differently?
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Table 5: Low Similarity Name Pair Checklist (i.e., combined score is $\leq 49\%$).

In most circumstances, these names are viewed as sufficiently different to minimize confusion. Exceptions to this would occur in circumstances where, for example, there are data that suggest a name with low similarity is nonetheless misinterpreted as a marketed product name in a prescription simulation study. In such instances, FDA would reassign a low similarity name to the moderate similarity category and review according to the moderately similar name pair checklist.

Appendix A1: Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

Appendix B: Prescription Simulation Results

FDA Prescription Simulation Responses (Aggregate 1 Rx Studies Report)

Study Name: Restasis Multidose

As of Date 10/20/2016

316 People Received Study
55 People Responded

Study Name: Restasis Multidose

Total	23	13	19	
INTERPRETATION	OUTPATIENT	VOICE	INPATIENT	TOTAL
RESTASIS	2	1	3	6
RESTASIS MULITDOSE	1	0	0	1
RESTASIS MULTI DOSE	0	2	0	2
RESTASIS MULTIDOSE	19	8	14	41
RESTASIS MULTI-DOSE	0	2	0	2
RESTASIS MUTLIDOSE	0	0	1	1
RESTASISMULTIDOSE	0	0	1	1
RESTATIS MULTIDOSE	1	0	0	1

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LISSA C OWENS
10/20/2016

MISHALE P MISTRY
10/21/2016

LUBNA A MERCHANT
10/21/2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50790Orig1s25

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



NDA 050790/ S-024
NDA 050790 /S-025

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Allergan, Inc.
2525 Dupont Drive
PO Box 19534
Irvine, CA 92623-9534

ATTENTION: Linda McCauley, Ph.D.
Manager, Global Regulatory Affairs

Dear Dr. McCauley:

Please refer to your Supplemental New Drug Applications (sNDAs) dated and received June 27, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cyclosporine Ophthalmic Emulsion, 0.05%.

We also refer to your correspondence, dated and received September 7, 2016, requesting review of your proposed proprietary name, Restasis MultiDose.

We have completed our review of the proposed proprietary name Restasis MultiDose and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your September 7, 2016 submission is altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

NDA 050790/ S-024

NDA 050790 /S-025

Page 2

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Abiola Olagundoye-Alawode, PharmD, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-3982. For any other information regarding this application, contact Jacquelyn E. Smith, Regulatory Project Manager in the Office of New Drugs, at (301) 796-1002.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

IRENE Z CHAN on behalf of TODD D BRIDGES
10/24/2016

**REQUEST FOR OPDP (previously DDMAC) LABELING REVIEW
CONSULTATION**

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

****Please send immediately following the Filing/Planning meeting****

TO: CDER-OPDP-RPM	FROM: (Name/Title, Office/Division/Phone number of requestor) Rhea Lloyd/ MO/William Boyd, MOTL Division of Transplant and Ophthalmology Products
-----------------------------	---

REQUEST DATE: 10/17/16	IND NO.	NDA/BLA NO. 50790/ S025	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
---------------------------	---------	----------------------------	---

NAME OF DRUG: Restasis® (cyclosporine ophthalmic emulsion) 0.05%	PRIORITY CONSIDERATION: PAS-Labeling Supplement	CLASSIFICATION OF DRUG N/A	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting)
---	--	-------------------------------	--

NAME OF FIRM: Allergan	PDUFA Date: October 27, 2016
---------------------------	------------------------------

TYPE OF LABEL TO REVIEW

TYPE OF LABELING: (Check all that apply) <input checked="" type="checkbox"/> PACKAGE INSERT (PI) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> CARTON/CONTAINER LABELING <input type="checkbox"/> MEDICATION GUIDE <input type="checkbox"/> INSTRUCTIONS FOR USE(IFU)	TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA <input type="checkbox"/> IND <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input checked="" type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	REASON FOR LABELING CONSULT <input type="checkbox"/> INITIAL PROPOSED LABELING <input checked="" type="checkbox"/> LABELING REVISION For OSE USE ONLY <input type="checkbox"/> REMS
---	--	---

EDR link to submission:

EDR Location: <\\CDSESUB1\evsprod\NDA050790\050790.enx>

EDR Location: <\\CDSESUB1\evsprod\NDA050790\0153>

Please Note: There is no need to send labeling at this time. OPDP reviews substantially complete labeling, which has already been marked up by the CDER Review Team. After the disciplines have completed their sections of the labeling, a full review team labeling meeting can be held to go over all of the revisions. Within a week after this meeting, "substantially complete" labeling should be sent to OPDP. Once the substantially complete labeling is received, OPDP will complete its review within 14 calendar days.

OSE/DRISK ONLY: For REMS consults to OPDP, send a word copy of all REMS materials and the most recent labeling to CDER DDMAC RPM. List out all materials included in the consult, broken down by audience (consumer vs provider), in the comments section below.

COMMENTS/SPECIAL INSTRUCTIONS:

A copy of the substantially complete PI is attached and a copy in Word format will be provided via email.

Mid-Cycle Meeting:

Labeling Meetings:

Wrap-Up Meeting:

SIGNATURE OF REQUESTER

SIGNATURE OF RECEIVER

METHOD OF DELIVERY (Check one)

eMAIL

HAND

8 Page(s) have been Withheld in Full as b4 (CCI/TS)
immediately following this page

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JACQUELYN E SMITH
10/17/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR PATIENT LABELING REVIEW CONSULTATION	
TO: CDER-DMPP-PatientLabelingTeam		FROM: (Name/Title, Office/Division/Phone number of requestor) Rhea Lloyd/ MO/William Boyd, MOTL/Division of Transplant and Ophthalmology Products	
REQUEST DATE: October 11, 2016	NDA/BLA NO.: 50790/ S-025	TYPE OF DOCUMENTS: (PLEASE CHECK OFF BELOW)	
NAME OF DRUG: Restasis® (cyclosporine ophthalmic emulsion) 0.05%	PRIORITY CONSIDERATION: PAS-Labeling Supplement	CLASSIFICATION OF DRUG: N/A	DESIRED COMPLETION DATE (Generally 2 Weeks after receiving substantially complete labeling)
SPONSOR: Allergan		PDUFA Date: October 27, 2016	
TYPE OF LABEL TO REVIEW			
TYPE OF LABELING: (Check all that apply) <input type="checkbox"/> PATIENT PACKAGE INSERT (PPI) <input type="checkbox"/> MEDICATION GUIDE <input checked="" type="checkbox"/> INSTRUCTIONS FOR USE(IFU)		TYPE OF APPLICATION/SUBMISSION <input type="checkbox"/> ORIGINAL NDA/BLA/ANDA <input type="checkbox"/> EFFICACY SUPPLEMENT <input type="checkbox"/> SAFETY SUPPLEMENT <input type="checkbox"/> LABELING SUPPLEMENT <input type="checkbox"/> MANUFACTURING (CMC) SUPPLEMENT <input type="checkbox"/> PLR CONVERSION	
REASON FOR LABELING CONSULT <input type="checkbox"/> INITIAL PROPOSED LABELING <input type="checkbox"/> LABELING REVISION			
EDR link to submission: EDR Location: \\CDSESUB1\evsprod\NDA050790\050790.enx EDR Location: \\CDSESUB1\evsprod\NDA050790\0153			
Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.			
COMMENTS/SPECIAL INSTRUCTIONS: Filing/Planning Meeting: [Insert Date(s)] Mid-Cycle Meeting: [Insert Date] Labeling Meetings: [Insert Dates] Wrap-Up Meeting: [Insert Date]			
SIGNATURE OF REQUESTER			
SIGNATURE OF RECEIVER			

Version: 06/06/2016

16 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JACQUELYN E SMITH
10/11/2016



NDA 50790/ S-024
NDA 50790/ S-025

COMPLETE RESPONSE –CMC/LABELING

Allergan, Inc.
Attention: Linda McCauley, PhD
Manager, Global Regulatory Affairs
2525 Dupont Drive
PO Box 19534
Irvine, CA 92623-9534

Dear Dr. McCauley:

Please refer to your Supplemental New Drug Application (sNDA) dated November 3, 2015, received November 3, 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for RESTASIS[®] (cyclosporine ophthalmic emulsion) 0.05%.

The resubmission dated June 27, 2016, received June 27, 2016, constitutes a complete response to our March 2 and May 2, 2016 action letters and the goal date is October 27, 2016.

If you have any questions, call me at (301) 796-1002.

Sincerely,

{See appended electronic signature page}

Jacquelyn Smith, MA
Senior Regulatory Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

JACQUELYN E SMITH
07/25/2016



NDA 50790/S-025

**ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT**

Allergan, Inc.
Attention: Kathrin Schalper, PhD, RAC
Senior Manager, Global Regulatory Affairs
2525 Dupont Drive
Irvine, CA 92612

Dear Dr. Schalper:

We have received your Supplemental New Drug Application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER: 50790
SUPPLEMENT NUMBER: 025
PRODUCT NAME: RESTASIS® (cyclosporine ophthalmic emulsion) 0.05%
DATE OF SUBMISSION: November 3, 2015
DATE OF RECEIPT: November 3, 2015

This supplemental application proposes separate Prescribing Information for the RESTASIS® Multi-Dose [REDACTED] (b) (4) Container Closure system and the existing unit dose presentation in order to minimize potential confusion for patients. The Instructions for Use differ significantly between the Multi-Dose [REDACTED] (b) (4) Container Closure system and the existing unit dose presentation.

Unless we notified you within 60 days of the receipt date that the application was not sufficiently complete to permit a substantive review, we filed the application on January 3, 2016, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>.

Please note that we have, for administrative reasons, split the above referenced supplement from CMC S-024, submitted on November 3, 2015.

The goal date for S-024 is March 3, 2016. The goal date for S-025 is May 3, 2016.

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Transplant and Ophthalmology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have questions, call me at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Jacquelyn Smith, MA
Senior Regulatory Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

JACQUELYN E SMITH
02/29/2016

REQUEST FOR CONSULTATION

TO (Division/Office):
Mail: OSE

FROM:
Laya Keyvan
OPQ
(240) 402-4598

DATE 12/16/2015	IND NO. N/A	NDA NO. 050790/S-024	TYPE OF DOCUMENT CMC Supplement (PAS)	DATE OF DOCUMENT 11/3/2015
NAME OF DRUG Restasis® (cyclosporine ophthalmic emulsion) 0.05%		PRIORITY CONSIDERATION PAS-CMC supplement	CLASSIFICATION OF DRUG N/A	DESIRED COMPLETION DATE 2/1/2016

NAME OF FIRM: Allergan Inc.

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE--NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input checked="" type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- | | |
|---|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILTY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> PRECLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS/SPECIAL INSTRUCTIONS:

Proposed changes: addition of an alternate container closure system for the drug product, "Multi-Dose (b) (4)

OSE/DMEPA review (new labeling is provided for the drug product, carton, container, and package insert)

SIGNATURE OF REQUESTER Laya Keyvan, MS, MBA	METHOD OF DELIVERY (Check all that apply) <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> DARRTS <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

06/18/2013

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/s/

LAYA KEYVAN
12/16/2015