

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

50790Orig1s24

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

50790Orig1s24

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Other Action Letters	X
Labeling	X
REMS	
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	X
Chemistry Review(s)	X
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology / Virology Review(s)	X
Clinical Pharmacology/Biopharmaceutics Review(s)	
Other Reviews	X
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	X
Administrative/Correspondence Document(s)	X

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50790Orig1s24

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

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
10/27/2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50790Orig1s24

OTHER ACTION LETTERS



NDA 50790/S-024

COMPLETE RESPONSE

Allergan, Inc.
Attention: Kathrin Schalper, PhD, RAC
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 a Multi-Dose (b) (4) (b) (4) Container Closure System. We have completed the review of your application, as amended, and have determined that we cannot approve this application in its present form because sterility cannot be assured for this Multi-Dose (b) (4) Container Closure System. Specifically,

1. We acknowledge the information regarding the dye ingress test to demonstrate content sterility during storage prior to first use; please provide the following additional information: a) the dye concentration in the immersion bath, b) the sensitivity of the detection method, and confirmation that the entry of approximately (b) (4) of dye into a challenge unit could be detected (upon dilution by the existing solution volume in the sample) by spectrophotometric assessment, and c) the data that support how said sensitivity and limit of detection were determined.
2. We acknowledge the information regarding the container closure integrity test to demonstrate content sterility during actuation (test 3A); please provide the incubation conditions (time and temperature) of the test and control units, and indicate (b) (4) (b) (4).
3. We acknowledge that the (b) (4) was carried out using (b) (4) samples of RESTASIS in the (b) (4) system; please clarify whether said samples were (b) (4) (b) (4) was agreed on at the May 2014 Type C (CMC) meeting. If the test containers differ from the ones agreed on at the referenced meeting, please justify.

4. We acknowledge the facility layouts depicting the manufacturing MD and UD processes; however, provide a brief narrative with the description of the manufacturing suite relevant to the commercial production of the multi-dose (b) (4) configuration of the drug product. The following information should also be provided: a) a floor plan(s) showing the location of the relevant areas associated with the manufacture of the subject drug product. When appropriate, said floor plan(s) should depict the room numbers/names and the location of the filling line for the drug product, as well as the location of any critical equipment used for the manufacture of the drug product, b) the air classification of each room involved in the manufacture of the drug product, as well as pressure differentials, and c) depiction of personnel, component and product flow.



b.

(b) (4)

c.

d.

e. Provide a complete list of validation and production acceptance criteria for the

(b) (4)

f. Provide the parameters used for (b) (4) of loads used for commercial production.

g. Provide the frequency and policy of requalification of the (b) (4) (b) (4) with regards to commercial manufacturing of the subject drug product.

8. Please provide the date of performance of the (b) (4) that relate to the (b) (4) manufacturing and filling processes (UD and MD areas).

9.

(b) (4)

(b) (4)

Provide additional supporting data as/if necessary.

10 (b) (4)

11. (b) (4)

12. Describe the actual routine and non-routine interventions that were performed during the (b) (4) performed during commercial production of the drug product in the proposed (b) (4) container closure system.

13. (b) (4)

14. Please state the filling speed used for commercial production.

15. (b) (4)

16. (b) (4)

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

We acknowledge that “alternate equipment of the same design and operating principle may be used with appropriate qualification, when there is no change in the approved process methodology or in process control limit”. However, please note that if any piece of equipment that is previously validated and further approved by the Agency is changed post-approval (i.e., model, capacity, etc.), the alternate equipment must be initially validated and the Agency should be notified as appropriate.

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 supplemental 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.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference 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's "Guidance for Industry - Formal Meetings Between the FDA and Sponsors or Applicants", May 2009 at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with this change before approval of this supplemental application.

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

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
03/02/2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50790Orig1s24

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

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

6.2 Post-marketing Experience

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Lactation

8.4 Pediatric Use

8.5 Geriatric Use

11 DESCRIPTION**12 CLINICAL PHARMACOLOGY**

12.1 Mechanism of Action

12.3 Pharmacokinetics

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.

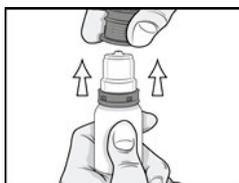


Do not use **RESTASIS MULTIDOSE™** if shipping cover or pull tab are damaged or missing.

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.



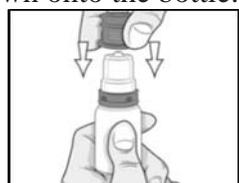
Step 3: Remove the olive green colored protective cap by pulling it straight up. Keep the colored protective cap.



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.

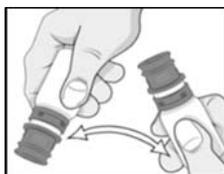


Step 5: The bottle is now ready for use. After use, recap the bottle with the olive green colored protective cap by pushing it straight down onto the bottle.



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.

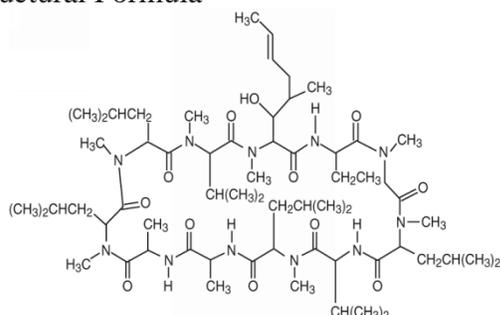
8.5 Geriatric Use

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.

© 2016 Allergan. All rights reserved.

Irvine, CA 92612, U.S.A.

All trademarks are the property of their respective owners.

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

Made in Ireland.

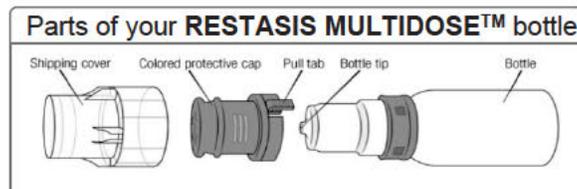


INSTRUCTIONS FOR USE
RESTASIS MULTIDOSE™ (Re stay' sis Mul tee dōs)
(cyclosporine ophthalmic emulsion) 0.05%

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.

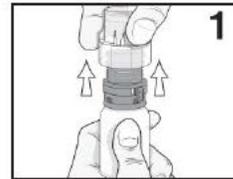
Important:

- **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:

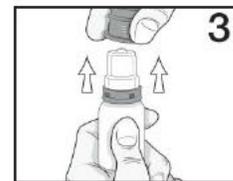
Step 1: Pull off shipping cover by pulling straight up. Throw the shipping cover away. **Do not use RESTASIS MULTIDOSE™** if shipping cover or pull tab are damaged or missing.



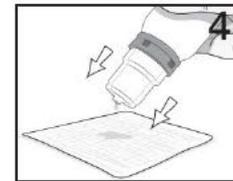
Step 2: Remove the pull tab on the olive green colored protective cap by pulling the end of the pull tab away from the bottle then winding it counterclockwise. Throw away the pull tab.



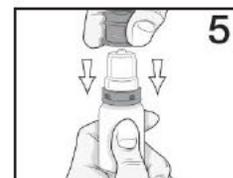
Step 3: Remove the olive green colored protective cap by pulling it straight up. Keep the colored protective cap.



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.



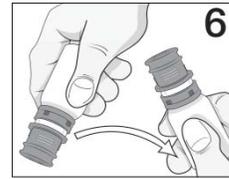
Step 5: The bottle is now ready for use. After use, recap the bottle with the olive green colored protective cap by pushing straight down onto the bottle.



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.

© 2016 Allergan. All rights reserved. Irvine, CA 92612, U.S.A.
All trademarks are the property of their respective owners. Patented: See: www.allergan.com/products/patents Made in Ireland.



Approved: 10/2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50790Orig1s24

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

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

/s/

RHEA A LLOYD
10/27/2016

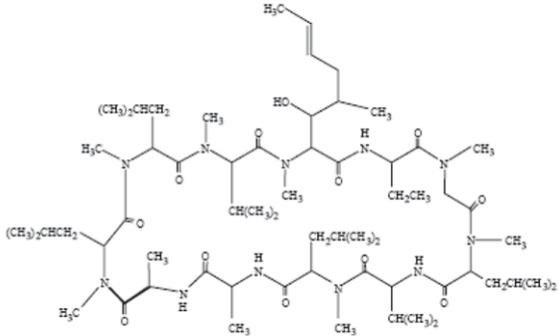
WILEY A CHAMBERS
10/27/2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50790Orig1s24

CHEMISTRY REVIEW(S)

Chemistry Review: # 2	1. Division: DTOP and DPMA1, OLDP/OPQ	2. NDA Number: 50-790
3. Name and Address of Applicant: Allergan Inc. 2525 Dupont Drive Irvine, CA 92612	4. Supplement(s): Number: S-024-RESUB-994 PA Date(s): June 27, 2016 Stamp Date: June 27, 2016 Due Date: October 27, 2016	
5. Name of Drug: RESTASIS®	6. Nonproprietary name: cyclosporine ophthalmic emulsion 0.05%	
7. PA Supplement Provides for: Addition of an alternate container closure system to the drug product “Multi Dose (b) (4) ”		8. Amendment(s): None
9. Pharmacological Category: Immuno-modulator and anti-inflammatory	10. How Dispensed: R _x	11. Related Documents: None
12. Dosage Form: Ophthalmic solution	13. Potency: 0.05%	
<p>14. Chemical Name and Structure: <i>cyclosporine, USP [USAN 1981]</i> Molecular Formula: C₆₂H₁₁₁N₁₁O₁₂, Molecular Weight: 1202.6 g/mol</p> <p>Cyclo{[(E)-(2S, 3R, 4R)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoyl]-L-2-aminobutyryl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl}</p> 		
<p>15. Comments: This supplement proposes the addition of an alternate container closure for the drug product, “ Multi Dose (b) (4) container closure”. The currently approved presentation for this drug product is packaged in a Uni-Dose (UD) Preservative Free container closure.</p> <p>All the CMC aspects of this application 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.</p> <p>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. See microbiology review in Panorama and in DARRTS.</p>		

16. Recommendations and Conclusion: All CMC outstanding issues in this supplement have been satisfactorily resolved. From the point of view of CMC, this supplement is recommended for **approval**.

17. Name: Libaniel Rodriguez, Ph.D., OPS/OLDP/DPMIAI/BII
Date:

Signature:

18. Concurrence: David Lewis, Ph.D., BC/OPS/OLDP/DPMIAI/BII
Date:

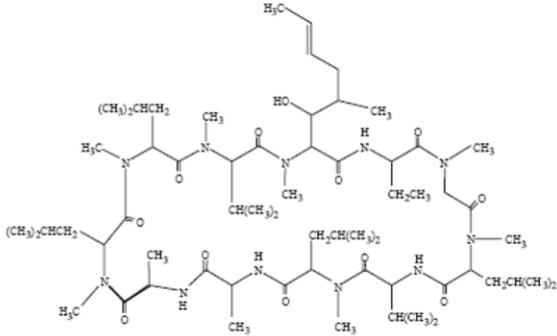
Signature:

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

/s/

LIBANIEL RODRIGUEZ
10/14/2016

DAVID B LEWIS
10/14/2016
concur; recommended for approval from the standpoint of CMC.

Chemistry Review: # 1	1. Division: DTOP and DPMA1, OLDP/OPQ	2. NDA Number: 50-790
3. Name and Address of Applicant: Allergan Inc. 2525 Dupont Drive Irvine, CA 92612	4. Supplement(s): Number: S-024; PA Date(s): November 3, 2016 Stamp Date: November 3, 2015 Due Date: March 3, 2016	
5. Name of Drug: RESTASIS®	6. Nonproprietary name: cyclosporine ophthalmic emulsion 0.05%	
7. PA Supplement Provides for: Addition of an alternate container closure system to the drug product "Multi Dose (b) (4) This supplement also requests the revision of the proprietary name RESTASIS® to RESTASIS® (b) (4) for the drug product in the proposed (b) (4)		8. Amendment(s): None
9. Pharmacological Category: Immuno-modulator and anti-inflammatory	10. How Dispensed: R _x	11. Related Documents: None
12. Dosage Form: Ophthalmic solution	13. Potency: 0.05%	
14. Chemical Name and Structure: Molecular Formula: C ₆₂ H ₁₁₁ N ₁₁ O ₁₂ , Molecular Weight: 1202.6 Cyclo {[(E)-(2S, 3R, 4R)-3-hydroxy-4-methyl-2-(methylamino)-6-octenoyl]-L-2-aminobutyryl-N-methylglycyl-N-methyl-L-leucyl-L-valyl-N-methyl-L-leucyl-L-alanyl-D-alanyl-N-methyl-L-leucyl-N-methyl-L-leucyl-N-methyl-L-valyl} 		
15. Comments: This supplement proposes the addition of an alternate container closure for the drug product, "Multi Dose (b) (4) container closure". The currently approved presentation for this drug product is packaged in a Uni-Dose (UD) Preservative Free container closure. The supplement also requests the revision of the current proprietary name RESTASIS® to RESTASIS® (b) (4) for the drug product in the proposed (b) (4). The composition and strength of cyclosporine ophthalmic emulsion 0.05% supplied in the new container closure system remain unchanged. Development of the proposed (b) (4) presentation has been extensively discussed, and agreed upon, with the agency during two Type C meetings held on February 8, 2012 and on May 15, 2014. The changes proposed in this supplement involve:		

- Product description with the new container closure.
- New manufacturing process development section for the filling process. This change involves Microbiological qualification studies, data and information on the (b) (4), process validation, sterilization for the single-use facility, and of the container closure and (b) (4). All the microbiological aspects of this application were sent to the microbiology review team for evaluation. **Dr, Yarery Smith from the microbiology review team examined the information provided and recommended the application for CR on February 25, 2016.**
- Removal for label leachable Acceptance Criterion at (b) (4), and submission of data on (b) (4) registration batches according to the proposed Specification.
- New stability summary and conclusion with (b) (4) specific data.
- New post-approval stability commitment.
- New stability data 12 plus months data on (b) (4) registration batches according to standard ICH condition.

Revision of the proprietary name from RESTASIS® to RESTASIS® (b) (4), as well as changes in the Package Insert and product labels were evaluated by the Clinical Division of DTOP and by OSE-DMEPA. Labeling changes will be reviewed upon satisfactory resolution of microbiology issues raised during this review cycle.

The manufacturing facility involved in this change, Allergan Pharmaceuticals, Ireland, was evaluated by the Office of Process and Facilities (OPF) and was recommended for approval on January 25, 2016. See copy of the OPF report attached at the end of this review.

16. Recommendations and Conclusion: The proposed, new Multi Dose (b) (4) applicator for the container closure, delivers consistently the desired droplet size and maintains sterility of the drug product through the length of stability studies reported in support of this application. All the construction materials utilized in the proposed applicator comply with 21 CFR (Food Contact Materials) as well as with USP and Ph. Eur. requirements. Overall, the proposed new (b) (4) applicator for this drug product performs as expected and it is suitable for its intended purposes. The manufacturing facility for the drug product utilizing the proposed applicator was recommended for approval by the Office of Process and facilities (OPF). From the Chemistry and manufacturing point of view, the (b) (4) container closure is acceptable. *However, the microbiology review raised deficiencies that need to be resolved prior to approval of this supplement. The overall recommendation from the CMC point of view is therefore, a Complete Response (CR) Letter, communicating the microbiology deficiencies to the applicant, and DMF deficiencies to the DMF (b) (4) holder. See microbiology reviews.*

17. Name: Libaniel Rodriguez, Ph.D., OPS/OLDP/DPMAl/BIl
Date:

Signature:

18. Concurrence: David Lewis, Ph.D., QL/OPS/OLDP/DPMAl/BIl signing for: Hasmukh Patel, Ph.D., DD/OPS/OLDP/DPMAl
Signature:

Date:

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

/s/

LIBANIEL RODRIGUEZ
02/26/2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50790Orig1s24

MICROBIOLOGY/VIROLOGY REVIEW(S)

Product Quality Microbiology Review

October 6, 2016

NDA: 050790/S-024

Drug Product Name

Proprietary: Restasis

Non-proprietary: cyclosporine ophthalmic emulsion 0.05%

Review Number: 2

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
06/27/2016	06/27/2016	N/A	07/13/2016
09/14/2016	09/14/2016	N/A	09/15/2016

Submission History (for amendments only) –

Submit Date(s)	Microbiology Review #	Review Date(s)
11/03/2015	1	02/25/2016

Applicant/Sponsor

Name: Allergan, Inc

Address: 2525 Dupont Dr., Irvine, CA 92612

Representative: Mirabelle Pao, Ph.D., Sr. Manager, Global Reg. Affairs

Telephone: 714-246-3292

Name of Reviewer: Yarery C. Smith, Ph. D.

Conclusion: The submission **is recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

- A. 1. **TYPE OF SUBMISSION:** Amendment for Prior Approval Supplement
2. **SUBMISSION PROVIDES FOR:** The original supplement submission provided for addition of a Multi-Dose (b) (4) Container Closure System. The subject review relates to the PAS amendments submitted on 06/27/2016 and 09/14/2016.
3. **MANUFACTURING SITE:**
Allergan Pharmaceuticals Ireland,
Castlebar Rd. Westport, County Mayo,
Ireland
4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Ophthalmic suspension, topical, 0.05%, in a single dose*, (b) (4).
- *The proposed container is intended for multiple dose.
5. **METHOD(S) OF STERILIZATION:** (b) (4)
6. **PHARMACOLOGICAL CATEGORY:** Indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with kerato-conjunctivitis sicca.
- B. **SUPPORTING/RELATED DOCUMENTS:**
- DMF (b) (4) is referenced for pertinent information regarding the (b) (4) (b) (4). A LOA (dated 08/10/2015) is provided. The relevant information has been reviewed in (b) (4) mic1a2.doc (Y. Smith, dated 10/06/2016) and was deemed adequate.
- C. **REMARKS:** This is an eCTD submission.

filename: 050790s24a1.doc

Executive Summary

I. Recommendations

- A. Recommendation on Approvability -**
NDA 50790/S-024 is recommended for approval on the basis of microbiological product quality.
- B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A**

II. Summary of Microbiology Assessments

- A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology –** The drug product is manufactured by (b) (4)
(b) (4)
(b) (4)
- B. Brief Description of Microbiology Deficiencies –** None identified
- C. Contains Potential Precedent Decision(s) -** **Yes** **No**
The container closure system for the subject NDA contains a dispenser which is designed to maintain the sterility of the multi-dose (b) (4) drug product during the recommended in-use period.

III. Administrative

- A. Reviewer's Signature** _____
- B. Endorsement Block**
Microbiologist/Yarey C. Smith, Ph.D.
Microbiology QAL (Acting)/John Metcalfe, Ph.D.
- C. CC Block**
N/A

Product Quality Microbiology Assessment

NDA 050790/S-024 provided for the addition of a Multi-Dose (b) (4) Container Closure System. There will be no changes to the active ingredient, formulation, in-process controls, analytical methods, reference standards and specifications, as currently approved.

The subject supplement amendment is in response to microbiology deficiencies conveyed to the Applicant in the Agency’s letter dated 03/02/2016 and 09/02/2016. The original deficiencies are italicized.

A. Microbiology Deficiencies:

- 1. We acknowledge the information regarding the dye ingress test to demonstrate content sterility during storage prior to first use; however, provide the following information: a) the dye concentration in the immersion bath, b) the sensitivity of the detection method, and confirmation that the entry of approximately (b) (4) of dye into a challenge unit could be detected (upon dilution by the existing solution volume in the sample) by spectrophotometric assessment, and c) the data that support how said sensitivity and limit of detection were determined.*

Response: The applicant stated that the dye concentration in the immersion bath was

(b) (4)

(b) (4)

Adequate data were provided to support the assessment of the sensitivity and limit of detection for the dye ingress test.

Acceptable

- 2. We acknowledge the information regarding the container closure integrity test to demonstrate content sterility during actuation (test 3A); however, provide the incubation conditions (time and temperature) of the test and control units, and indicate (b) (4)*

Response: The applicant stated that the test and control samples were incubated at 30 – 35°C for 3 days.

(b) (4)

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

/s/

YARERY C SMITH
10/11/2016

JOHN W METCALFE
10/11/2016
I concur.

Product Quality Microbiology Review

February 25, 2016

NDA: 050790/S-024

Drug Product Name

Proprietary: Restasis

Non-proprietary: cyclosporine ophthalmic emulsion 0.05%

Review Number: 1

Dates of Submission(s) Covered by this Review

Submit	Received	Review Request	Assigned to Reviewer
11/03/2015	11/03/2015	N/A	12/18/2016

Applicant/Sponsor

Name: Allergan, Inc

Address: 2525 Dupont Dr., Irvine, CA 92612

Representative: Kathrin Schalper, Sr. Manager, Global Reg. Affairs

Telephone: 714-246-4188

Name of Reviewer: Yarery C. Smith, Ph. D.

Conclusion: The submission **is not recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

- A. 1. **TYPE OF SUBMISSION:** Prior Approval Supplement
2. **SUBMISSION PROVIDES FOR:** Addition of Multi-Dose Preservative-Free (MDPF) Container Closure System.
3. **MANUFACTURING SITE:**
Allergan Pharmaceuticals Ireland,
Castlebar Rd. Westport, County Mayo,
Ireland
4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Ophthalmic suspension, topical, 0.05%, in a single dose* (b) (4)
- *The proposed container is intended for multiple dose.
5. **METHOD(S) OF STERILIZATION:** (b) (4)
6. **PHARMACOLOGICAL CATEGORY:** Indicated to increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with kerato-conjunctivitis sicca.

B. **SUPPORTING/RELATED DOCUMENTS:**

NDA 050790/S-019 (reviewed by S. Donald in N050790s19.doc, dated 11/29/2012)

Microbiology memo n050790memor1-4-30-14.doc is referenced for the minutes from a May 2014 Type C (CMC) meeting between the Agency and the applicant regarding the briefing package for NDA 050790 RESTASIS® in the MDPF container closure system.

DMF (b) (4) is referenced for pertinent information regarding the (b) (4) (b) (4)A LOA (dated 08/10/2015) is provided. The relevant information has been reviewed i (b) (4) mic1.doc (Y. Smith, dated 02/17/2016) and was deemed inadequate.

- C. **REMARKS:** This is an eCTD submission.

filename: 050790s24.doc

Executive Summary

I. Recommendations

- A. **Recommendation on Approvability -**
NDA 50790/S-024 is not recommended for approval on the basis of microbiological product quality.
- B. **Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A**

II. Summary of Microbiology Assessments

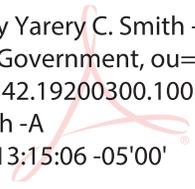
- A. **Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology –** The drug product is manufactured by (b) (4)
(b) (4)
(b) (4).
- B. **Brief Description of Microbiology Deficiencies –**
See Section 3 of this review.
- C. **Contains Potential Precedent Decision(s) -** Yes No

III. Administrative

- A. **Reviewer's Signature** _____
- B. **Endorsement Block**
Microbiologist/Yarery C. Smith, Ph.D.
Microbiology QAL (Acting)/John Metcalfe, Ph.D.
- C. **CC Block**
N/A

4 SIGNATURE PAGE

Digitally signed by Yarery C. Smith -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People, 0.9.2342.19200300.100.1.1=2000584216,
cn=Yarery C. Smith -A
Date: 2016.02.25 13:15:06 -05'00'



**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50790Orig1s24

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING

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)

Date of This Memorandum: October 27, 2016
Requesting Office or Division: Division of Transplant and Ophthalmology Products (DTOP)
Application Type and Number: NDA 050790/S-024
Product Name and Strength: Restasis MultiDose (Cyclosporine Ophthalmic Emulsion)
0.05%
Submission Date: October 26, 2016
Applicant/Sponsor Name: Allergan
OSE RCM #: 2016-1535
DMEPA Primary Reviewer: Lissa Owens, PharmD
DMEPA Team Leader: Mishale Mistry, PharmD, MPH

1 PURPOSE OF MEMO

Division of Transplant and Ophthalmology Products (DTOP) requested that we review the revised container label and carton labeling for Restasis MultiDose (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The revised label and labeling can be improved to increase clarity and maintain consistency with the instructions for use.

3 RECOMMENDATIONS FOR ALLERGAN

We recommend the following be implemented prior to approval of this NDA:

^a Owens, L. Label and Labeling Review for Restasis MultiDose (NDA 050790). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 Oct 24. 9 p. OSE RCM No.: 2016-1535.

A. Carton Labeling

1. To maintain consistency with the revised Instructions for Use, we recommend revising the carton labeling instructions as follows:

PREPARING THE BOTTLE FOR FIRST-TIME USE



1. Pull off and throw away shipping cover.
DO NOT USE IF SHIPPING COVER OR PULL TAB IS DAMAGED OR MISSING.
2. Remove and throw away pull tab.
3. Remove and keep the colored protective cap.
4. Prime the bottle for first time use by squeezing 2 drops onto a tissue.
5. The bottle is now ready for use. After use, recap the bottle with the colored protective cap.

REMEMBER BEFORE EACH USE TO TURN THE BOTTLE UPSIDE DOWN A FEW TIMES TO MAKE SURE THE MEDICINE IS MIXED WELL

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

1. As the Dosage and Administration section is intended for Health Care Providers, we recommend you revise the statement ‘your dose’ to ‘the dose’ in Step 6.

2 Page(s) of Draft Labeling has 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/

LISSA C OWENS
10/27/2016

MISHALE P MISTRY
10/27/2016

LABEL AND LABELING 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 24, 2016
Requesting Office or Division: Division of Transplant and Ophthalmology Products (DTOP)
Application Type and Number: NDA 050790/S-025
Product Name and Strength: Restasis MultiDose (Cyclosporine Ophthalmic Emulsion)
0.05%
Product Type: Single-Ingredient Product
Rx or OTC: Rx
Applicant/Sponsor Name: Allergan
Submission Date: September 7, 2016
OSE RCM #: 2016-1535
DMEPA Primary Reviewer: Lissa Owens, PharmD
DMEPA Team Leader: Mishale Mistry, PharmD, MPH

1 REASON FOR REVIEW

This review responds to a request from the Division of Transplant and Ophthalmology Products (DTOP) to review a Labeling Prior Approval Supplement (PAS) for Restasis MultiDose*** (NDA 050790/S-025) as part of a response to CMC comments received in a Complete Response on March 2, 2016. The CMC PAS proposes to add a multi-dose, preservative free container closure system to the existing single-dose presentation of Restasis. OPQ requested that DMEPA review the proposed labels and labeling to determine if there are any areas of vulnerability from a medication error perspective.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Allergan submitted a Labeling PAS as resubmission to a Complete Response dated March 2, 2016. In this PAS, Allergan proposes a new container closure system of a multiple dose, preservative-free bottle presentation of Restasis (cyclosporine ophthalmic emulsion). Allergan proposes to market the product under a different proprietary name and separate Prescribing Information. The proposed proprietary name, Restasis Multidose***, is under review by DMEPA. A preservative-free single-use vial under the proprietary name, Restasis, is currently available on the market.

The proposed product will contain Instructions for Use on the carton labeling and attached to the end of the Prescribing Information on how to open and prepare the bottle for first-time use. Specifically, the proposed product requires priming before initial use. Section 2 Dosage and Administration includes instructions on how to prepare the bottle for first time use and for subsequent uses. In addition, the proposed product will be supplied in different packaging consisting of a dispenser (applicator tip, protective cap, and shipping cover) and bottle as

compared to the existing single-use low-density polyethylene vial of Restasis. The proposed product also has a [REDACTED] (b) (4), compared to the current Restasis product which is single-dose and remaining contents should be discarded immediately after administration. However, the composition, strength, indication, route, formulation, and dosing of the proposed product does not differ from the currently marketed Restasis.

We note that the Division of Medical Policy Programs has provided recommendations for the Instructions for Use for Restasis MultiDose. We reviewed the proposed label and labeling and noted that the prominence of important information can be increased on the carton labeling and in the prescribing information to promote the safe use of the product. Therefore, we provide recommendations for the Division in Section 4.1 and for the Applicant in Section 4.2.

4 CONCLUSION & RECOMMENDATIONS

We reviewed the label and labeling and identified that the proposed carton labeling and prescribing information can be improved to increase the prominence of important information to promote the safe use of the product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. 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.
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.

4.2 RECOMMENDATIONS FOR ALLERGAN

We recommend the following be implemented prior to approval of this NDA:

A. Container Label and Carton Labeling

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

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 [REDACTED] (b) (4) [REDACTED] (b) (4)
2. Include the term “Multiple Dose” to improve clarity and ensure that the product is safely used and handled.
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.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Restasis MultiDose that Allergan submitted on September 7, 2016.

Table 2. Relevant Product Information for Restasis and Restasis MultiDose		
	Restasis	Restasis MultiDose(proposed)
Approval Date	December 23, 2002	N/A
Active Ingredient	Cyclosporine	
Indication of Use	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.	
Route of Administration	Ophthalmic	
Dosage Form	Ophthalmic emulsion	
Strength	0.5 mg/mL	
Dose and Frequency	Instill one drop twice daily (approximately 12 hours apart) in each eye	
How Supplied	<p>Sterile, preservative-free single-use vials.</p> <p>Each vial contains 0.4 mL fill in a 0.9 mL LDPE vial; 30 or 60 vials are packaged in a polypropylene tray with an aluminum peelable lid. The entire contents of each tray (30 vials or 60 vials) must be dispensed intact.</p>	<p>Sterile, multi-dose preservative-free bottle.</p> <p>Each bottle consists of a white opaque LDPE bottle, a white opaque polypropylene top with (b) (4) unidirectional valve and air filter technology, a protective olive green polypropylene cap, and a clear disposable shipping cover over the colored cap. 5.5 mL in 10-mL bottle (30-day supply).</p>
Storage	15°-25°C (59°-77°F).	(b) (4)

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on October 4, 2016 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. In addition, we limited our case search to reports that listed 'Restasis' as the primary suspect, eliminated cases of dose omission, and limited the time frame to 2016. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.^a

Date Range	January 1, 2016 to October 4, 2016
Product	Restasis
Event (MedDRA Terms)	DMEPA Official FBIS Search Terms Event List: Contraindicated Drug Administered (PT) Drug Administered to Patient of Inappropriate Age (PT) Inadequate Aseptic Technique in Use of Product (PT) Medication Errors (HLGT) Overdose (PT) Prescribed Overdose (PT) Prescribed Underdose (PT) Product Adhesion Issue (PT) Product Compounding Quality Issue (PT) Product Formulation Issue (PT) Product Label Issues (HLT) Product Packaging Issues (HLT) Product Use Issue (PT) Underdose (PT)

E.2 Results

Our search retrieved 348 cases, but after further evaluation, we didn't identify any medication error cases that were relevant for this review and could be addressed by labels and labeling revisions.

E.4 Description of FAERS

^a The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

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 G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^b along with postmarket medication error data, we reviewed the following Restasis MultiDose labels and labeling submitted by Allergan on September 7, 2016.

- Carton labeling
- Container label
- Professional Sample Carton Labeling
- Professional Sample container label
- Instructions for Use (no image)

G.2 Label and Labeling Images

Carton labeling

(b) (4)



^b Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

(b) (4)

Container label

(b) (4)

Currently Marketed Restasis:

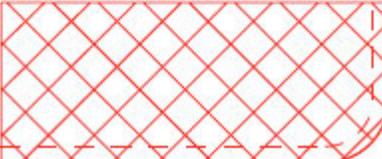
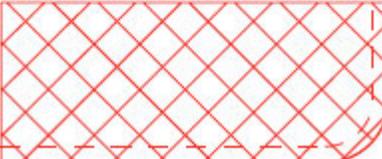
NDC 0023-9163-60
No. 94529



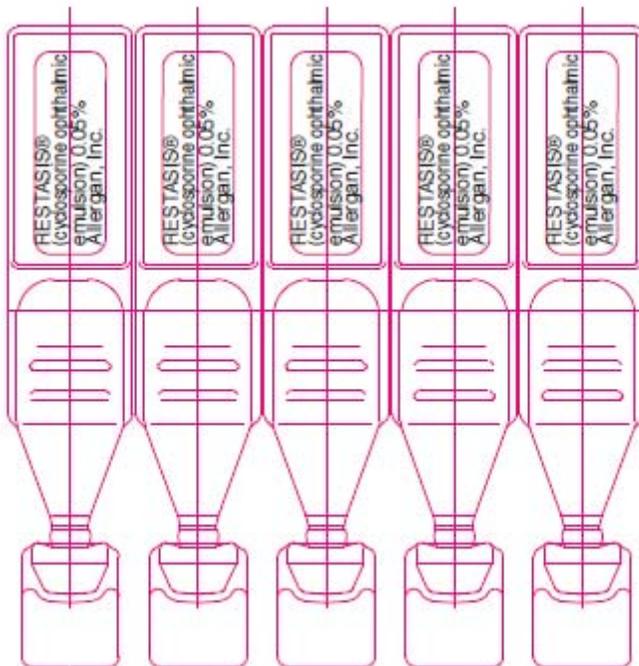
60 Single-Use Vials (0.4 mL each) One Month Supply **Sterile, Preservative-Free**

Each mL contains: **Active:** cyclosporine 0.05% **Inactives:** glycerin; castor oil; polysorbate 80; carbomer copolymer type A; purified water; and sodium hydroxide to adjust pH.

Usual Dosage: Twice daily approximately 12 hours apart. Invert the vial before using. Use immediately after opening and then discard. **Storage:** Store at 15°-25° C (59°-77° F). Store vials in the thermoformed tray until use. The entire contents of each package (60 vials) must be dispensed intact.

© 2013 Allergan, Inc., Irvine, CA 92612, U.S.A. Lot: 
® marks owned by Allergan, Inc. Exp.: 
Patented. See: www.allergan.com/products/patent_notices
Made in the U.S.A.

 **ALLERGAN** Rx only 55091US10



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
10/24/2016

MISHALE P MISTRY
10/25/2016

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Drug Utilization Review**

Date: September 16, 2016

Reviewer(s): Corinne Woods, RPh, MPH
Division of Epidemiology II

Acting Team Leader LCDR Justin Mathew, PharmD
Division of Epidemiology II

Deputy Director
for Drug Utilization LCDR Grace Chai, PharmD
Division of Epidemiology II

Subject: Restasis[®] Drug Utilization Information

Drug Name(s): Restasis[®]

Application Types/Numbers: NDA 021023, NDA 050790

Applicant/Sponsor: Allergan, Inc.

OSE RCM #: 2016-1857

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.****

Table of Contents

1	Introduction.....	1
1.1	Background	1
1.2	Product Information	1
2	Methods and Materials.....	1
2.1	Determining settings of care	1
2.2	Methodology	1
3	Results.....	1
3.1	Projected annual patient counts.....	1
3.2	Projected annual prescription counts.....	2
4	Discussion	2
5	Conclusion	3
6	References.....	3
7	Appendices.....	4
7.1	Appendix A: Data Tables and Figures	4
7.2	Appendix B: Database Descriptions	7

1 INTRODUCTION

1.1 BACKGROUND

On August 16, 2016 the Office of Prescription Drug Promotion (OPDP) within the U.S. Food and Drug Administration (FDA) requested information regarding utilization of Restasis[®], a prescription product. The request was prompted by a submission by the Sponsor of Restasis[®] for two proposed promotional items claiming "Restasis[®], prescribed for (b) (4) patients since 2003". The Sponsor provided the source data to OPDP (see *Table 1 in Appendix A*), and OPDP has requested comparable information in order to verify the Sponsor's claim.

1.2 PRODUCT INFORMATION

The FDA approved Restasis[®] in December 2002 to treat suppressed tear production presumed due to ocular inflammation associated with keratoconjunctivitis sicca. The product is available as 30-day or 60-day unit-of-use packages.¹

2 METHODS AND MATERIALS

This analysis was conducted using proprietary drug utilization databases available to FDA. See *Appendix B* for detailed descriptions and limitations of the databases used.

2.1 DETERMINING SETTINGS OF CARE

The IMS Health, IMS National Sales PerspectivesTM database was used to determine the retail and non-retail channels of distribution for Restasis[®] included in this analysis. From July 2010 through May 2016, sales data for Restasis[®] indicated that approximately (b) (4) % of packages/bottles were distributed to outpatient retail pharmacies, (b) (4) % to mail order pharmacies and (b) (4) % to non-retail settings.^a As a result, the utilization patterns of Restasis[®] examined in this review were focused on outpatient retail pharmacy and mail order/specialty pharmacy settings. Non-retail data were not included in this analysis.

2.2 METHODOLOGY

IMS Health, Total Patient TrackerTM database was used to provide a national estimate of the annual number of unique patients who were dispensed prescriptions for Restasis[®] from outpatient U.S. retail pharmacies from January 2003 through May 2016. IMS Health, National Prescription AuditTM were used to provide a national estimate of the annual number of dispensed prescriptions for Restasis[®] from outpatient U.S. retail pharmacies and mail order/specialty pharmacies from January 2006 through May 2016.

3 RESULTS

3.1 PROJECTED ANNUAL PATIENT COUNTS

Table 2 and Figure 1 in Appendix A display data showing the nationally projected number of patients who received dispensed prescriptions for Restasis[®] from U.S. outpatient retail pharmacies annually from 2003 through May 2016. Annual projected patient counts increased

^a IMS Health, IMS National Sales PerspectivesTM. July 2010 to May 2016. Extracted August 2016. File: NSP 2016-1857 Restasis 8.24.2016.xlsx.

steadily during the time examined, from approximately (b) (4) patients in 2003 to (b) (4) patients in 2015. These annual projected patient counts, which include prescriptions dispensed from U.S. outpatient retail pharmacies, are 7-25% lower than the annual projected patient counts provided by the Sponsor.

3.2 PROJECTED ANNUAL PRESCRIPTION COUNTS

Table 3 in Appendix A displays data from IMS Health, National Prescription Audit™ showing the nationally projected number of dispensed prescriptions for Restasis® from U.S. outpatient retail pharmacies annually from 2006 through May 2016. Annual projected prescription counts increased during the time examined, from approximately (b) (4) prescriptions in 2006 to (b) (4) prescriptions in 2015. A total of approximately (b) (4) prescriptions were dispensed during this time period, including prescriptions dispensed from U.S. outpatient retail pharmacies as well as mail-order/specialty pharmacies. With the exception of 2016, the annual projected prescription counts were similar to the annual projected prescription counts provided by the Sponsor.

4 DISCUSSION

This analysis provides data regarding Restasis® utilization for a comparison to utilization data supplied by the Sponsor. Using the IMS Health Total Patient Tracker™ data, we found that the projected annual patient counts were 7-25% lower than the projected patient counts provided by the Sponsor. However, the IMS data included patients who received Restasis® prescriptions from outpatient retail pharmacies, while the data provided by the Sponsor included outpatient retail as well as mail order/specialty pharmacies. After accounting for this difference, the projected annual patient counts provided by the Sponsor appear roughly similar to the IMS-sourced estimations of projected annual patient counts. All of the estimates provided in this review were projected national estimates, but no statistical tests were performed to determine statistical significant changes over time or between products. Consequently, all changes over time should be considered approximate.

Compared to aggregated patient counts, aggregated prescription counts are a more robust metric for evaluating product exposure over larger periods of time, due to the lower potential for double-counting of unique patients. For example, a patient may be double counted if they received prescriptions at different time periods from different pharmacies. Using the IMS National Prescription Audit™, we estimated a projected total of (b) (4) Restasis® prescriptions were dispensed from January 2006 through May 2016, which is comparable to the aggregated totals provided by the Sponsor. The IMS-sourced projected annual prescription counts for Restasis® were also similar to the projected prescription counts provided by the Sponsor, with overall differences ranging less than 10%. The IMS-sourced data and Sponsor-provided data both included prescriptions dispensed from outpatient retail pharmacies as well as mail order/specialty pharmacies.

The Sponsor provided an estimated aggregate count of patients who received Restasis® from January 2003 through May 2016. This was calculated in a two-step process: (1) calculating the ratio of unprojected *unique* patient counts to unprojected *aggregated* prescription counts, and (2) applying this ratio to the aggregated projected prescription counts. The Sponsor provided no documentation as to the validity or robustness of this mix-and-match methodology of comparing unique counts to aggregated sums. Across the years, these calculated ratios are similar, ranging

from 1.6 to 2.4. However, the ratio for all of the years combined is well beyond this range at 4.8, a red flag for possible faulty logic in manipulating the drug utilization statistics.

The Sponsor cited an aggregated, unprojected total of (b) (4) Restasis® patients from 2003 through May 2016. However, they provided no details regarding the methodology for linking patient data across time. It is assumed that the Sponsor's data source utilized various patient attributes—including geographical attributes—and payer attributes to link claims over time to a particular patient. It is also assumed that the completeness and quality of data that is available at the patient level is variable across claims and across time. Given that record linkage is highly sensitive to the quality of the underlying data being linked, there are limitations to linking data across a large timespan. For example, patients' names and birthdates may be misrepresented, and patients may move geographic locations as well as health plan insurers. If too many patient identifiers are used to link claims across time, a patient who moved locations and/or health care plans may be misrepresented as two separate patients. Thus, a linked record may not be created and the patient could be double-counted. Conversely, if too few patient identifiers are used, different patients' records may be misrepresented as the same patient. Thus, an incorrect linked record may be created. For these reasons and more, it is highly inadvisable to aggregate unique patient counts without a valid and robust quality control methodology in place. Preferable methods include reporting the estimated annual unique patient counts, or the total aggregated number of prescriptions dispensed.

5 CONCLUSION

In response to the request from OPDP, the Department of Epidemiology-II cannot support the aggregated patient count analysis provided by the Sponsor based on the methods and data sources provided. Because aggregating unique patient counts over a span of many years using the data source and methods provided is not recommended, we suggest using annual unique patient counts or aggregated prescription counts. To this end, our results showed somewhat lower annual patient counts than the projected patient counts provided by the Sponsor. We estimate that a total of (b) (4) prescriptions for Restasis have been dispensed from retail and mail-order pharmacies since 2006, somewhat less than the aggregated prescription count provided by the Sponsor.

6 REFERENCES

1. Allergan Inc. Restasis® [package insert]. Irvine, CA. 2013.

7.2 APPENDIX B: DATABASE DESCRIPTIONS

IMS Health, IMS National Sales Perspectives™: Retail and Non-Retail

The IMS Health, IMS National Sales Perspectives™ measures the volume of drug products, both prescription and over-the-counter, and selected diagnostic products moving from manufacturers into various outlets within the retail and non-retail markets. Volume is expressed in terms of sales dollars, eaches, extended units, and share of market. These data are based on national projections. Outlets within the retail market include the following pharmacy settings: chain drug stores, independent drug stores, mass merchandisers, food stores, and mail service. Outlets within the non-retail market include clinics, non-federal hospitals, federal facilities, HMOs, long-term care facilities, home health care, and other miscellaneous settings.

IMS Health, Total Patient Tracker™ (TPT)

Total Patient Tracker (TPT) is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting over time. TPT derives its data from the Vector One® database which integrates prescription activity from a sample received from payers, switches, and other software systems that may arbitrage prescriptions at various points in the sales cycle. Vector One® receives over 2.1 billion prescription claims per year.

IMS Health, National Prescription Audit™

The National Prescription Audit (NPA™) measures the “retail outflow” of prescriptions, or the rate at which drugs move out of retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers via formal prescriptions in the U.S. The NPA audit measures what is dispensed by the pharmacist. Data for the NPA audit is a national level estimate of the drug activity from retail pharmacies. NPA™ receives over 3.5 billion prescription claims per year, captured from a sample of the universe of approximately 59,400 pharmacies throughout the U.S. The pharmacies in the database account for most retail pharmacies and represent nearly 88% of retail prescriptions dispensed nationwide. The type of pharmacies in the sample are a mix of independent, retail, chain, mass merchandisers, and food stores with pharmacies, and include prescriptions from cash, Medicaid, commercial third-party and Medicare Part-D prescriptions. Data is also collected from approximately 45 - 75% (varies by class and geography) of mail service pharmacies and approximately 70-85% of long-term care pharmacies. Data are available on-line for 72- rolling months with a lag of 1 month. Data is also collected from approximately 40 - 70% (varies by class and geography) of mail service pharmacies and approximately 45-55% of long-term care pharmacies. Data are available on-line for 72- rolling months with a lag of 1 month.

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

/s/

CORINNE M WOODS
09/16/2016

JUSTIN A MATHEW
09/16/2016

GRACE CHAI
09/16/2016

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

50790Orig1s24

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

Contents

1	INTRODUCTION.....	1
1.1	Regulatory History.....	1
1.2	Product Information.....	1
2	RESULTS.....	1
2.1	Misbranding Assessment.....	1
2.2	Safety Assessment.....	2
3	CONCLUSIONS.....	4
3.1	Comments to the Applicant.....	5
4	REFERENCES.....	6
	APPENDICES.....	7

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, 2106 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)

^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?
--	--	--

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:

50790Orig1s24

**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



NDA 050790/S-024

**PROPRIETARY NAME REQUEST
ACKNOWLEDGEMENT/WITHDRAWAL**

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 Application (sNDA) dated June 27, 2016, 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 September 1, 2016, correspondence, received on September 1, 2016, notifying us that you are withdrawing your request for a review of the proposed proprietary name, Restasis (b)(4). Therefore, Restasis (b)(4) is considered withdrawn as of September 1, 2016.

Finally, we refer to your September 7, 2016, correspondence, received September 7, 2016, requesting review of your proposed proprietary name, Restasis MultiDose. Upon preliminary review of your submission, we have determined that it is a complete submission as described in the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>

Therefore, the user fee goal date is December 6, 2016.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet Higgins, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-0330. 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}

Janet G. Higgins
Safety Regulatory Project Manager
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/

JANET G HIGGINS
10/07/2016

MEMORANDUM of TELECONFERENCE

MEETING DATE: August 31, 2016
TIME: 2:00 PM to 2:30 PM EST
LOCATION: WO 22; Rm. 2201
APPLICATION: NDA 050790/ S-024
DRUG NAME: cyclosporine ophthalmic emulsion, 0.05%
TYPE OF MEETING: Discussion of PNR

MEETING CHAIRS: Lubna Merchant, MS, PharmD, Deputy Division Director
Mishale Mistry, PharmD, MPH, Team Leader

FDA ATTENDEES:

Office of Surveillance and Epidemiology

Janet Higgins, *Senior Regulatory Project Manager*

Office of Medication Error Prevention and Risk Management, Division of Medication Error Prevention Analysis (DMEPA)

Lubna Merchant, MS, PharmD, *Deputy Division Director*

Mishale Mistry, PharmD, MPH, *Team Leader*

Lissa Owens, PharmD, *Safety Evaluator*

Division of Transplant and Ophthalmology (DTOP)

Wiley Chambers, MD, *Deputy Division Director*

Jacqueline Smith, *Senior Regulatory Project Manager*

SPONSOR ATTENDEES:

(b) (6)	Medical Safety Physician for RESTASIS
Wilmar Estrada	Director, Advertising and Promotional Compliance
Dawn Koffler	Sr. Director, Strategic Marketing
Linda McCauley, PhD	Manager, Global Regulatory Affairs
Sesha Neervannan, PhD	Sr Vice President, Pharmaceutical Development
Roshni Babaria, PharmD	Sr Specialist, Global Labeling Compliance
Michael Robinson, MD	Vice President, Therapeutic Area Head
Kathrin Schalper, PhD	Director, Project Management
Sai Shankar, MS	Director, Package Engineering
Paul Stone, PhD	Sr Director, Global Regulatory Affairs

BACKGROUND:

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. On November 3, 2015, the Applicant submitted the name, Restasis (b) (4) for our review; however, a complete response was issued for the application on March 2, 2016. At the time of re-submission, the Applicant submitted the name Restasis (b) (4) for review.

MEETING OBJECTIVES:

The purpose of the call was to let Sponsor know that DMEPA has completed their preliminary review of the name and has some concerns.

DMEPA CONCERNS WITH THE PROPOSED NAME:

DMEPA asked the Applicant to clarify if they had studies which support healthcare individuals' understanding of the proposed modifier (b) (4). The Applicant stated that there were such studies performed by the (b) (4) for the modifier (b) (4) but not for (b) (4). DMEPA stated that there are some concerns, as the proposed modifier (u) (4), is not currently used in the marketplace. In the submission, the Applicant stated that the purpose of the modifier (b) (4) is to distinguish the single dose vials from the proposed multiple dose bottles. However, even though healthcare providers are familiar with the modifier (b) (4), healthcare providers may not be familiar with the (u) (4) of the proposed modifier to indicate (b) (4). Additionally, DMEPA stated that although, in the marketplace, there are products using the modifier (b) (4). These products are single dose products and therefore, (b) (4) in the modifier, healthcare providers may not realize that this product is multi-dose.

REGULATORY OPTIONS

DMEPA options for sponsor to consider amending the submission to 'Restasis Multidose' or "Restasis" and use labels and labeling to indicate that the product is 'preservative-free'.

DISCUSSION

The Applicant stated that they would be withdrawing the pending proprietary name and proposing a new name, Restasis Multidose. There was also concern that this name might not be reviewed at the same time as the action of the pending supplement. DMEPA stated that they understand the concern and will work closely with DTOP and try to evaluate the name and provide a response prior to the action date of the supplement.

OSE referred the Applicant to the guidance for Proprietary Name Review submissions to assure that the Applicant properly label their submissions to assure quick processing.

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

/s/

JANET G HIGGINS
09/14/2016



NDA 50790/S-024

**PROPRIETARY NAME
ACKNOWLEDGEMENT**

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 Application (sNDA) dated June 27, 2016, received June 27, 2016, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cyclosporine Ophthalmic Emulsion, 0.05%.

We acknowledge receipt of your June 27, 2016, correspondence, received June 27, 2016, requesting a review of your proposed proprietary name, Restasis (b) (4)

The user fee goal date is September 25, 2016.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Janet Higgins, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-0330. 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}

Janet Higgins
Safety Regulatory Project Manager
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/

JANET G HIGGINS
07/25/2016



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

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
07/25/2016

REQUEST FOR CONSULTATION

TO (Division/Office):

Mail: OSE

FROM: Chinedu Ebonine, RBPM, OPQ/OPRO/DPMA1, 240-402-3448

DATE
07/05/2016

IND NO.
N/A

NDA NO.
50-790

TYPE OF DOCUMENT
S-024

DATE OF DOCUMENT
06/27/2016

NAME OF DRUG
Restasis® (cyclosporine
ophthalmic emulsion) 0.05%

PRIORITY CONSIDERATION
PAS-CMC supplement

CLASSIFICATION OF DRUG
N/A

DESIRED COMPLETION DATE
8/27/2016

NAME OF FIRM:

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- DISSOLUTION
 BIOAVAILABILTY STUDIES
 PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
 PROTOCOL-BIOPHARMACEUTICS
 IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

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
Chinedu Ebonine, PharmD.

METHOD OF DELIVERY (Check all that apply)
 MAIL DARRTS HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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

/s/

CHINEDU I EBONINE
07/05/2016

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

- TYPE A OR B NDA REVIEW
 END OF PHASE II MEETING
 CONTROLLED STUDIES
 PROTOCOL REVIEW
 OTHER (SPECIFY BELOW):

- CHEMISTRY REVIEW
 PHARMACOLOGY
 BIOPHARMACEUTICS
 OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- DISSOLUTION
 BIOAVAILABILITY STUDIES
 PHASE IV STUDIES

- DEFICIENCY LETTER RESPONSE
 PROTOCOL-BIOPHARMACEUTICS
 IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
 DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
 CASE REPORTS OF SPECIFIC REACTIONS (List below)
 COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP

- REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
 SUMMARY OF ADVERSE EXPERIENCE
 POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

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)
 MAIL DARRTS HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

06/18/2013

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

/s/

LAYA KEYVAN
12/16/2015