CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

021537Orig1s019

Trade Name:	Ciprodex
Generic or Proper Name:	Ciprofloxacin and Dexamethasone
Sponsor:	Novartis Pharmaceuticals Corp
Approval Date:	May 27, 2022
Indication:	For the treatment of infections caused by susceptible isolates of the designated microorganisms in: 1. Acute Otitis Media (AOM) in pediatric patients (age 6 months and older) with tympanostomy tubes due to *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis, and Pseudomonas aeruginosa*. 2. Acute Otitis Externa (AOE) in pediatric (age 6 months and older), adult, and elderly patients due to *Staphylococcus aureus and Pseudomonas aeruginosa*.

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021537Orig1s019

CONTENTS

Reviews / Information Included in this NDA Review.

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

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APPLICATION NUMBER:

021537Orig1s019

APPROVAL LETTER

NDA 021537/S-019

APPROVAL LETTER

Novartis Pharmaceuticals Corp
Attention: Jason Lantvet
Regulatory CMC Associate Director - Regulatory Affairs GDD CMC
One Health Plaza
Bldg 337/04/B19L2-31
East Hanover, NJ 07936

Dear Mr. Lantvet:

Please refer to your Supplemental New Drug Application (sNDA) dated and received December 15, 2021, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for CIPRODEX (ciprofloxacin and dexamethasone) otic suspension.

This "Changes Being Effected in 30 days" supplemental new drug application provides for:

Addition of alternate sterilization sites for the (b) (4) sterilization of the drug product primary packaging components as follows:

- (b) (4)
-

APPROVAL

We have completed our review of this supplemental application. This supplement is approved.

We remind you that you must comply with reporting requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Megan Nguyen, Regulatory Business Process Manager, at Megan.Nguyen@fda.hhs.gov or (301) 796 - 7826.

Sincerely,

{See appended electronic signature page}

David B. Lewis, Ph.D.
Branch Chief, B2
Division of Post-Marketing Activities I
Office of Lifecycle Drug Products
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

David Lewis

Digitally signed by David Lewis
Date: 5/27/2022 08:15:45AM
GUID: 508da72000029f287fa31e664741b577

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021537Orig1s019

CHEMISTRY REVIEW(S)

Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls

1. **NDA Supplement Number:** NDA-021537-SUPPL-19
   sNDA Recommendation: Approval
   sNDA Managed by: OPQ

2. **Submission(s) Being Reviewed**:

Submission	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Original Supplement	CBE-30	12/15/2021	12/15/2021	12/16/2021	06/15/2022	05/26/2022

3. **Provides For From Cover Letter:** Addition of alternate sterilization sites for the (b) (4) (b) (4) sterilization of the drug product primary packaging components as follows:
   - (b) (4)
   -

4. **Review #**: 1

5. **Clinical Review Division**: OID/DAI

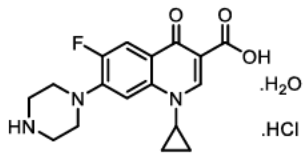
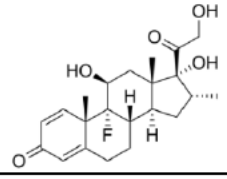
6. **Name and Address of Applicant**:
   Novartis Pharmaceuticals Corporation
   One Health Plaza
   East Hanover, NJ 07926-1080

   Phone: 862-778-8300
   Email: jason.lantvet@novartis.com

7. **Drug Product**:

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product
CIPRODEX® (ciprofloxacin and dexamethasone) otic suspension	Otic Suspension	0.3% / 0.1%	Otic	Rx	No

8. **Chemical Name and Structure of Drug Substance**:

	**USAN:** Ciprofloxacin Hydrochloride USP **Chemical Name:** 1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid, monohydrochloride, monohydrate **Molecular Formula:** $C_{17}H_{18}FN_3O_3 \cdot HCl \cdot H_2O$ **MW:** 385.82
	**USAN:** Dexamethasone, USP **Chemical Name:** 9-fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione **Molecular Formula:** $C_{22}H_{29}FO_5$ **MW:** 392.46

9. Indication: Treatment of:

- Acute Otitis Media in pediatric patients (age 6 months and older) with tympanostomy tubes due to *Staphylococcus aureus, Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis*, and *Pseudomonas aeruginosa*.
- Acute Otitis Externa in pediatric (age 6 months and older), adult and elderly patients due to *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

10. Supporting/Related Documents: Microbiology review (23-MAR-2022)

11. Disciplines/Consults:

Disciplines/Consults	Recommendation	Date	Reviewer
OPMA/Facility	Approval (No Evaluation Necessary)	12-JAN-2022	Allison A. Aldridge, Ph.D.
OPMA/Microbiology	Approval	23-MAR-2022	Amanda D. Buskirk, Ph.D.

12. Executive Summary:

With this CBE-30 supplemental application, the applicant proposes to add (b) (4) in (b) (4) as alternative sites for the (b) (4) sterilization of the primary packaging components (b) (4) used for the drug product, Ciprodex® (ciprofloxacin and dexamethasone) otic suspension.

The Office of Pharmaceutical Manufacturing Assessment (OPMA) decided on "No Evaluation Necessary" for the proposed primary packaging sterilization sites, and an overall manufacturing inspection recommendation (OMIR) was issued on 12-JAN-2022 for approval.

The validation data supporting the sterilization of the drug product primary packaging components by (b) (4) at the proposed sites were found adequate in the Microbiology review. The submission was recommended for approval from a Quality Microbiology perspective.

Based on the OPMA and Microbiology recommendations of approval, the addition of drug product primary packaging sterilization sites are acceptable from a CMC perspective.

13. Conclusions & Recommendations:

This supplement is recommended for approval.

14. Comments/Deficiencies to be Conveyed to Applicant: None

15. Primary Reviewer:
Ramesh Gopalaswamy, Ph.D., CMC reviewer, Branch 2, DPMAI, OLDP, OPQ

16. Secondary Reviewer:
David B. Lewis, Ph.D., Branch Chief, Branch 2, DPMAI, OLDP, OPQ

CMC Assessment

I. Background Information

CIPRODEX® (ciprofloxacin and dexamethasone) otic suspension (*NDA-021537 approved 18-JUL-2003*) is a combination of ciprofloxacin, a broad-spectrum fluoroquinolone antibacterial and dexamethasone, an anti-inflammatory corticosteroid. Each mL of Ciprodex otic suspension contains ciprofloxacin hydrochloride (equivalent to 3 mg ciprofloxacin base), 1 mg dexamethasone, and 0.1 mg benzalkonium chloride as a preservative. The inactive ingredients are boric acid, sodium chloride, hydroxyethyl cellulose, tyloxapol, acetic acid, sodium acetate, edetate disodium, and purified water. Sodium hydroxide and/or hydrochloric acid may be added for adjustment of the pH.

CIPRODEX is a white-to off-white suspension supplied as follows: 7.5 mL fill in a (b) (4) (b) (4) system. The (b) (4) system consists of a natural polyethylene bottle and natural plug, with a white polypropylene closure. Tamper evidence is provided with a shrink band around the closure and neck area of the package.

Currently, (b) (4) performs the (b) (4) sterilization of the drug product primary packaging components (b) (4). This supplement provides addition of alternative sterilization sites for the sterilization of the drug product primary packaging.

II. Proposed Changes

The Applicant, Novartis Pharmaceuticals, proposes to add alternative sterilization sites for the (b) (4) sterilization of the drug product primary packaging components as follows:

1) (b) (4)
2)

III. Assessment of Data Submitted to Support the Proposed Changes

3.2.P Drug Product:

3.2.P.3. Manufacture

P.3.1. Manufacturers: This section was revised to provide an updated list of facilities responsible for the manufacture of Ciprodex drug product as shown in the table below.

Updated Facilities Information for Ciprodex Otic Suspension

Site Information	Responsibilities
Alcon-Couvreur NV Rijksweg 14 2870 Puurs Belgium FEI: 3002037047 DUNS: 370205429	(b) (4)
Alcon Research LLC (dba Alcon Laboratories, Inc. and fully owned subsidiary of Alcon Laboratories, Inc.)	

Site Information	Responsibilities
6201 South Freeway Fort Worth, TX 76134 FEI: 1610287 DUNS: 007672236	(b) (4)

(b) (4)

Evaluation: ***Adequate***

The Office of Pharmaceutical Manufacturing Assessment (OPMA) decided on "No Evaluation Necessary" for the proposed primary packaging sterilization sites, (b) (4) and (b) (4) and an overall manufacturing inspection recommendation (OMIR) was issued on 12-JAN-2022 for approval. Screen shot regarding the OPMA OMIR is reproduced below:

(b) (4)

(b) (4)

P.3.5. Process Validation and/or Evaluation: Validation reports of supporting the proposed addition of the primary packaging sterilization sites, (b) (4) were included in this scetion.

Evaluation: ***Adequate***

The validation data supporting the sterilization of the drug product primary packaging components (bottle, plug and cap) by (b) (4) at the proposed sites were assessed by Microbiology reviewer Amanda D. Buskirk, Ph.D. (OPQ/OPMA/DMAII) and were found adequate. The supplement submission was recommended for approval from a Quality Microbiology perspective. Refer to the Microbiology review for full details (Panorama file: N021537S019MR01.docx; 23-MAR-2022).

Environmental Assessment

In section 1.11.1. Quality Information Amendment of this submission, the applicant, citing 21 CFR Part 25.31(a), requested a categorical exclusion from the requirements to prepare an Environmental Assessment for this submission covering an addition of primary packaging sterilization sites.

Evaluation: ***Adequate***

Based on the applicant statement that the addition of primary packaging sterilization sites will not increase the use of the active moiety, and that to the best of the applicant's knowledge, no extraordinary circumstance exists, which may significantly affect the quality of the human environment, the request for the categorical exclusion from the requirements to prepare an Environmental Assessment may be granted.

IV. Risk Associated with the Proposed Changes and Impact to Product Quality and Patient Safety

Low. Based on the OPMA and Microbiology recommendations of approval, the addition of drug product primary packaging sterilization sites are not expected adversely impact the quality and performance of the Ciprodex drug product.

Ramesh Gopalaswamy

Digitally signed by Ramesh Gopalaswamy
Date: 5/26/2022 04:07:33PM
GUID: 56a003a70000dc95f354c8051d776163

David Lewis

Digitally signed by David Lewis
Date: 5/26/2022 04:08:04PM
GUID: 508da72000029f287fa31e664741b577
Comments: concur; recommend approval from the standpoint of CMC

Initial Quality Assessment - OLDP Division of Post-Marketing Activities I

NDA: 021537 **Supplement:** 19	**Applicant:** Novartis Pharmaceuticals, Corp.	**Product:** CIPRODEX® (ciprofloxacin and dexamethasone) otic suspension
Clinical Division: DAI		
Managed by: OND ☐ *Efficacy* ☐ *Labeling* ☐		**OPQ** ☒
Receipt Date: 12/15/2021		**PDUFA Goal Date: 6/15/2022**
Proposed changes: addition of two alternate facilities for (b) (4) sterilization of container closure components (b) (4)		
Complete Response: Yes ☐ No ☒		
Submitted Category: CBE-0 ☐ CBE-30 ☒ PA ☐		**Final Category:** CBE-0 ☐ CBE-30 ☒ PA ☐

Expedited Review Requested:	**Drug Shortage:**	**Group Supplements:**
Yes ☐ No ☒	Yes ☐ No ☒	Yes ☐ No ☒

Other Disciplines:

Facility: ☒	Micro: ☒	[1]Biopharm: ☐	Pharm/tox: ☐
Statistics: ☐	OPF: ☐	DMEPA: ☐	Clin Pharm: ☐
DMF: ☐	CDRH/ODE ☐	CDRH/OC ☐	[2]Formulation Change ☐

Other:

Comments: this CBE-30 supplement provides for the addition of an alternate facility to perform (b) (4) sterilization (b) (4)

Present primary packaging sterilization sites (b) (4)		Proposed primary packaging sterilization sites	
Sterilization site	*Components*	*Sterilization site*	*Components*
		(b) (4)	

In addition, a new function is added for an approved facility (b) (4) (b) (4)

This supplement requires a consult to the microbiology staff.

(b) (4)

QAL: David Lewis	**Date:** 12/22/2021
Assigned Reviewer: Ramesh Gopalaswamy	**RBPM:** Megan Nguyen

[1]Refer to the MOU between OLDP and ONDP for scenarios that require Biopharm consult.

[2]Notify Andre Raw and copy DD & BC and request for a Biopharm reviewer.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021537Orig1s019

MICROBIOLOGY REVIEW(S)

CBE Microbiology Review Form

03-22-2022

Applicant: Novartis Pharmaceuticals Corporation Type of Supplement: CBE-30

NDA/Supplement #: 021537 Supplement 19

Drug Product Name: CIPRODEX® (ciprofloxacin)

Receipt Date: 12/15/2021

Manufacturing Site: (b) (4)

Method of Sterilization: (b) (4)

Dosage Form, Route of Administration and Strength/Potency: Otic Suspension/0.3% ciprofloxacin and 0.1% dexamethasone

File Name: N021537S019MR01.docx

Proposed Change(s): Addition of alternative (b) (4) sterilization site for the primary container closure system (b) (4)

Supporting/Related Documents:

Conclusion:

☒ The supplement is recommended for approval

☐ Information requested (deficiencies to be conveyed to the applicant are listed at the end of the review)

Template: CBE Review Form.doc

Review Notes:
This CBE-30 supplement proposes the addition of the following 2 (b) (4) facilities for sterilization of the container closure system (CCS), (b) (4)

1. (b) (4)
2.

The CCS used for Ciprodex 0.3% + 0.1% Ear drops, suspension is currently sterilized via (b) (4) (b) (4) It is noted that the (b) (4) of the CCS for the approved drug product.

Per pg. 4 of 7 in the "Summary of Changes…" in Section 1.11.1, editorial changes were made to the "registered documentation" located in Section 3. Section 3.2.P.3.1 includes updated information for the proposed (b) (4) facilities and all other sites involved in manufacturing, packaging, and testing of the approved drug product. Section 3.2.P.3.5 contains the document "Process Validation and (or) Evaluation…," which summarizes the validation and evaluation (b) (4) for Ciprodex otic suspension manufactured at Alcon's Aspex Manufacturing Facility (Fort Worth, TX) and the Alcon-Couvreur Manufacturing Facility (Puurs, Belgium). The applicant states that there are no changes to the drug product composition, quality of drug substance, excipients, or the primary CCS. The "Process Validation and (or) Evaluation…" document was updated to include the proposed (b) (4) sites. Validation data supporting the proposed changes are assessed below.

(b) (4)

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

Conclusion: Adequate – The applicant has met regulatory expectations for validating the process used for sterilization of the subject container closure system at the proposed additional sterilization facilities.

Primary Reviewer: Amanda D. Buskirk, Ph.D.

Secondary Reviewer: Erika Pfeiler, Ph.D.

Amanda Buskirk

Digitally signed by Amanda Buskirk
Date: 3/23/2022 09:58:05AM
GUID: 5abd30fe012d54e0c7daec7dadcf7381

Erika Pfeiler

Digitally signed by Erika Pfeiler
Date: 3/23/2022 10:00:18AM
GUID: 502d1da500002b6a73a00c0e0dff6e1d

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

021537Orig1s019

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 05/27/2022 08:43:52 AM
To: JASON.LANTVET@NOVARTIS.COM
CC:
BCC: megan.nguyen@fda.hhs.gov
Subject: NDA 021537/S-019 Action Letter

Hello,

Attached is the official copy of your action letter for this sNDA. Please confirm receipt of this email to Megan.Nguyen@fda.hhs.gov.

Thanks,

Division of Regulatory Business Process Management III Office of Program and Regulatory Operations Office of Pharmaceutical Quality FDA

Please find the attached documents below:

NDA-021537-SUPPL-19_Upload Final Decision_Approved.pdf

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

Sent: 12/30/2021 06:53:37 AM
To: JASON.LANTVET@NOVARTIS.COM
CC:
BCC: megan.nguyen@fda.hhs.gov
Subject: NDA ACKNOWLEDGEMENT - CBE SUPPLEMENT

Please see attached.

Please find the attached documents below:

NDA-021537-SUPPL-19_Acknowledgement Letter.pdf

NDA 021537/S-019

CBE SUPPLEMENT - ACKNOWLEDGEMENT

Novartis Pharmaceuticals Corp
Attention: Jason Lantvet
Regulatory CMC Associate Director - Regulatory Affairs
One Health Plaza
Bldg 337/04/B19L2-31
East Hanover, NJ 07936

Dear Mr. Lantvet:[1]

We have received your supplemental new drug application (sNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA or the Act) for the following:

NDA NUMBER:	021537
SUPPLEMENT NUMBER:	019
PRODUCT NAME:	CIPRODEX® (ciprofloxacin and dexamethasone) otic suspension
DATE OF SUBMISSION:	December 15, 2021
DATE OF RECEIPT:	December 15, 2021

This supplemental application, submitted as a "Changes Being Effected in 30 Days" supplement, proposes the following change:

> Addition of two alternate facilities for (b) (4) sterilization of container closure components (b) (4)

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 13, 2022, in accordance with 21 CFR 314.101(a).

If the application is filed, the user fee goal date will be June 15, 2022.

Cite the application number listed above at the top of the first page of all submissions to this application.

If you have any questions, please contact me at (301) 796 - 7826.

Sincerely,

{See appended electronic signature page}
Megan Nguyen
Regulatory Business Process Manager
Division of Regulatory and Business Process Management III (DRBPMIII)
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Megan Nguyen

Digitally signed by Megan Nguyen
Date: 12/30/2021 06:51:54AM
GUID: 60da4bb30012f3b7f9fb15d75a45618d