CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213978Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
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 7, 2021
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	NDA 213978
Product Name and Strength:	Tyrvaya (varenicline tartrate) Nasal Spray, (b) (4) per spray
Applicant/Sponsor Name:	Oyster Point Pharmaceuticals (Oyster Point)
OSE RCM #:	2020-2679
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD
DMEPA Associate Director for Nomenclature and Labeling:	Mishale Mistry, PharmD, MPH

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised Prescribing Information, Patient Information, Instructions for Use, container labels, and carton labeling received on October 5, 2021 for Tyrvaya. The Division of Ophthalmology (DO) requested that we review the revised labels and labeling for Tyrvaya (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to the multidisciplinary label and labeling comments communicated to the Applicant.[a,b,c]

2 DISCUSSION

We note with the revised labels and labeling that the previously proposed proprietary name (PPN), (b) (4) *** is replaced. The Applicant withdrew the PPN, (b) (4) *** and a subsequent proprietary name request for the PPN, Tyrvaya, was received August 18, 2021. The PPN, Tyrvaya, was found conditionally acceptable on October 1, 2021 under OSE RCM # 2021-

[a] Flint, J. Human Factors, Label, and Labeling Review for Varenicline (NDA 213978). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 AUG 09. RCM No.: Insert RCM Number Or Other Review Identifier.
[b] Semidey, D. FDA Communication: NDA 213978 Labeling. Silver Spring (MD): FDA, CDER, DO (US); 2021 OCT 01. NDA 213978.
[c] Nguyen M and Newcomer C. Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU) for varenicline (NDA 213978). Silver Spring (MD): FDA, CDER, DMPP, OPDP (US); 2021 SEP 01. NDA 213978.

1044724132.[d] Thus, the labels and labeling have been updated to reflect the Applicant's conditionally acceptable PPN, Tyrvaya. Additionally, of note, the Applicant proposes to change the strength from (b) (4) per spray to (b) (4) per spray throughout the labels and labeling. The Applicant indicates that this change in strength is "(b) (4) " We inquired from DO if the change in strength is acceptable. As part of their review of the revised labeling, DO conveyed to us that the strength presentation would be revised from (b) (4) to 0.03 mg to address the Applicant's concerns. Thus, we note that the strength will need to be revised throughout the labels and labeling to ensure consistency.

Beyond the above mentioned changes, we note that the revised labels and labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 3 for the Division and in Section 4 for Oyster Point Pharmaceuticals.

3 RECOMMEDATIONS FOR DIVISION OF OPHTHALMOLOGY (DO)

Table 1. Identified Issues and Recommendations for Division of Ophthalmology (DO)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information			
Full Prescribing Information – Section 2 Dosage and Administration			
(b) (4)			

[d] Birkemeier, D. Proprietary Name Review for Tyrvaya (NDA 213978). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 OCT 01. PNR ID #.: 2021-1044724132.

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

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON OCTOBER 5, 2021

Prescribing Information

- Prescribing Information (Image not shown) available from: \\CDSESUB1\evsprod\nda213978\0032\m1\us\proposed-tc.docx

Patient Information and Instructions for Use

- Patient Information and Instructions for Use (Image not shown) available from: \\CDSESUB1\evsprod\nda213978\0032\m1\us\pt-info-instructions-use-tc.docx

Container Labels

- Commercial – container label

(b) (4)

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

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

VALERIE S VAUGHAN
10/07/2021 11:55:38 AM

MISHALE P MISTRY
10/08/2021 01:09:11 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration

Center for Drug Evaluation and Research
Office of New Drugs, ODE-IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9855

MEMORANDUM TO FILE

Date of Consult Request:	8/19/2021
From:	The Division of Ophthalmology (DO)
To:	Division of Pediatric and Maternal Health (DPMH)
NDA Number:	213978
Drug:	Varenicline nasal spray
Applicant:	Oyster Point Pharma
Indication:	Dry Eye Disease

DO submitted a consult request to DPMH on 8/19/2021, for a 505(b)(2) original NDA submission. The RLD is Chantix which has unexpired pediatric related exclusivity. The Applicant has listed Paragraph IV Certification and has a licensing agreement with the patent owner AND the owner provided a written statement that it does not object to FDA's approval of the 505(b)(2) application.

Due to the unexpired pediatric exclusivity, DO would like to request this consult for any labeling considerations for NDA 213978.

DPMH pediatrics commented that there's no pediatric information to comment on.

DPMH pediatrics has no further comments at this time, thus, this memorandum will close out the consult request.

DPMH DDD:	John Alexander
DPMH MTL:	Shetarra Walker
DPMH Reviewer:	Ethan Hausman
DPMH RPM:	Denise Pica-Branco
DPMH SCSO:	Rosemary Addy

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

DENISE J PICA-BRANCO
09/30/2021 01:30:34 PM

Clinical Inspection Summary

Date	September 13, 2021
From	Ling Yang, M.D., Ph.D., FAAFP Min Lu, M.D., M.P.H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Jennifer Harris, M.D., Medical Officer William Boyd, M.D., Clinical Team Leader Dheera Semidey, Regulatory Health Project Manager Division of Ophthalmology
NDA #	213978
Applicant	Oyster Point Pharma, Inc.
Drug	(b) (4) (OC-01; varenicline tartrate) Nasal Spray
NME (Yes/No)	No
Review Priority	Standard
Proposed Indication(s)	Treatment of signs and symptoms of dry eye disease
Consultation Request Date	February 1, 2021
Summary Goal Date	August 01, 2021; extended to September 18, 2021
Action Goal Date	September 17, 2021
PDUFA Date	October 17, 2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Clinical data from Studies ONSET-1 (OPP-002) and ONSET-2 (OPP-101) were submitted to the Agency in support of this New Drug Application (NDA) 213978 for (b) (4) (OC-01; varenicline tartrate) nasal spray for the proposed indication of treatment of signs and symptoms of dry eye disease. Two clinical investigators (CIs): Dr. David Wirta (Site #82 for Study OPP-002 and Site #30 for Study OPP-101), and Dr. Blair Boehmer (Site #81 for Study OPP-002 and Site #49 for Study OPP-101) were selected for clinical inspections.

The inspections verified the sponsor Oyster Point Pharma, Inc. (Oyster) submitted clinical data with source records at the CI sites. Based on the results of these CI inspections, Studies ONSET-1 (OPP-002) and ONSET-2 (OPP-101) appear to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

II. BACKGROUND

Oyster submitted NDA 213978 for (b) (4) (OC-01; varenicline tartrate) nasal spray on 12/17/2020. The proposed indication is for the treatment of signs and symptoms of dry eye disease. Data from two clinical studies ONSET-1 (OPP-002) and ONSET-2 (OPP-101) were submitted to support the approval of the NDA.

Study ONSET-1 (OPP-002)

Study ONSET-1 (OPP-002) was a Phase 2b, multicenter, randomized, double-masked, placebo-controlled study to evaluate the safety and efficacy of OC-01 (varenicline) nasal spray in adult subjects with dry eye disease (DED).

The study objective was to evaluate the safety and effectiveness of OC-01 nasal spray as compared to placebo with respect to signs and symptoms of DED. The primary efficacy endpoint was the change in Schirmer's Test Score (STS) from baseline to Day 28.

The study consisted of 5 visits in 30 days. At Visit 1, eligible subjects were randomized to one of the four treatment groups: placebo (vehicle) or low dose OC-01 (0.12 mg/mL) or medium dose OC-01 (0.6 mg/mL) or high dose OC-01 (1.2 mg/mL); and received the first dose of the study drug. At Visit 4, subjects received their first daily dose of the study drug during Controlled Adverse Environment (CAE® exposure) model. At Visits 2, 3, and 5 the first daily dose of study drug was administered in the office concurrent with Schirmer's Testing, while the second daily dose was self-administered at home. Between clinic visits, subjects self-administered the study drug: a single 50 µL intranasal spray in each nostril twice a day.

The study screened a total of 263 subjects, randomized 182 subjects in 3 study sites in the US. The first subject was enrolled on 08/15/2018, and the last subject completed the study on 09/26/2018.

Study ONSET-2 (OPP-101)

Study ONSET-2 (OPP-101) was a Phase 3, multicenter, randomized, controlled, double-masked study to evaluate the safety and efficacy of OC-01 (varenicline) nasal spray 0.6 mg/mL and 1.2 mg/mL in adult subjects with DED.

The primary study objective was to evaluate the safety and effectiveness of OC-01 (varenicline) nasal spray as compared to placebo on signs and symptoms of DED.

The primary efficacy endpoint was the percent of subjects who achieved ≥10 mm improvement in the study eye on STS from baseline at Week 4 (Visit 4b).

The study consisted of 7 visits in about 28 days. At Visit 1, eligible subjects were randomized in a 1:1:1 ratio to one of the 3 treatment groups: 0.6 mg/mL OC-01 nasal spray, 1.2 mg/mL OC-01 nasal spray or placebo (vehicle) nasal spray; and received the first dose of the study drug. At Visit 4a, subjects received their first daily dose of the study drug during CAE® exposure. At Visits 3 and 4b, the first daily dose of study drug was administered in the office concurrent with Schirmer's Testing, while the second daily dose was self-administered at home. Between clinic visits, subjects self-administered the study drug twice daily for 28 days with three additional long-term follow-up visits at 6 weeks, 6 months, and 12 months.

The study randomized a total of 758 subjects in 22 study sites in the US. The first subject was enrolled on July 23, 2019, and the study was ongoing as the study report cutoff date of August 28, 2020. The estimated last subject's last visit was in March 2021.

Rationale for Site Selection

Two CIs: Drs. David Wirta (Site #82 for Study OPP-002 and Site #30 for Study OPP-101) and Blair Boehmer (Site #81 for Study OPP-002 and Site #49 for Study OPP-101) were requested for inspection in support of the application. These sites were selected based on enrolling a high number of patients to the study treatment arms that may have an impact in the review division's clinical decision-making process.

III. RESULTS

1. David Wirta, M.D., Site 82 for Study OPP-002 and Site 30 for Study OPP-101

520 Superior Ave. Suite 235
Newport Beach, CA 92663

This CI was inspected on 08/2-13/2021 as a data audit for Studies OPP-002 and OPP-101 under the current NDA, in together with (b) (4) Study 1883-301-013 under NDA 214028. This is the 6th inspection for Dr. Wirta. Previous inspections were in 02/2002 with voluntary action indicated (VAI) due to the informed consent form (ICF) failed to include one planned test procedure (PK blood drawn); 08/2004 with no action indicated (NAI), 03/2006 with NAI; 05/2011 with NAI and 11/20/2015 with NAI.

For Study OPP-002, the study site screened a total of 90 subjects and enrolled 75 subjects, with 73 subjects completed the study. Two subjects withdrew the study after visit 1 due to adverse events (AEs): Subject # (b) (6) due to tinnitus, headache, and eyelid edema; and Subject # (b) (6) due to aggressive sneezing and burning throat. The first subject was enrolled on 08/27/2018 and the last subject's last visit was on 01/28/2021. All source records were reviewed for 25 of the 75 enrolled subjects.

For Study OPP-101, the study site screened a total of 97 subjects and enrolled 75 subjects, with 72 subjects completed the study. The first subject was enrolled on 07/23/2019 and the last subject's last visit was on 01/18/2021. All source records were reviewed for 25 of the 75 enrolled subjects.

Source records reviewed during the inspection included the study protocol and amendments, ICFs, documentation of eligibility criteria and enrollment logs, medical records (including visit data, monitoring logs, laboratory tests, AEs and concomitant medication use), the investigational product (IP) accountability records, subject diaries, paper case report forms (CRFs) with electronic CRFs (eCRFs) and the electronic database capture (EDC) enters/audits, protocol deviations, records retention and related regulatory documents [e.g., institutional review board (IRB) approvals and communications, staff training logs, ClinicalTrials.gov registration, financial disclosures and delegation of authority].

The inspection found adequate source documentation for inspected study subjects, with no significant deficiencies reported. The submitted data were verifiable with source records at the study site. The primary efficacy data source was verified. There was no evidence of underreporting of AEs.

At the end of the inspection, a Form 483 (Inspectional Observations) was issued for failure to prepare or maintain adequate and accurate case histories with respect to observations and data pertinent to the investigation.

Specifically,

For Study OPP-101, 12 (Subjects # (b) (6)) of the 25 inspected subjects were enrolled in other clinical studies (shown in the Table below) during the study's safety follow up period, which was after study visit 4b but prior to the last study visit. The investigational drugs taken by the subjects in the other studies were not reported in the eCRFs as concomitant medications.

Table 1: Summary of the 12 Subjects' Co-Enrollment in Other Clinical Studies During the Safety Follow-up Period of Study OPP-101

Subject #	Date of Last Study Dose	Date Subject Randomized in Other Studies	Time Between the Last Dose & Randomization in Another Study	Date of Last Visit
(b) (6)			4 months	(b) (6)
			4 months	
			4 months	
			4 months 7 months	
			6 months	
			6 months 9 months	
			4 months 6 months 9 months	
			4 months 6 months 9 months	
			4 months 9 months	

(b) (6)		(b) (6)
	4 months	
	7 months	
	8 months	
	4 months	

Reviewer's Comments:
The study consisted of a treatment period of 28 days and a safety follow up period of 12 months. Per the study protocol, "concurrent enrollment in another investigational drug or device study during the treatment period is not permitted". The study protocol did not prohibit subjects from participating in other clinical studies during the safety follow up period as #20 of the exclusion criteria stated, "Be currently enrolled in an investigational drug or device study or have used an investigational drug or device within 30 days prior to Visit 1 and during the treatment period". Thus, it is acceptable that subjects were co-enrolled in other clinical studies during the long-term safety follow-up period. However, all other IPs used during the following up period should be reported as concomitant medications as the protocol required that "The use of any concurrent medication, prescription or over-the-counter, is to be recorded on the subject's source document and corresponding eCRF along with the reason the medication was taken". The CI responded to FDA 483 on 08/31/2021 that 54 of the 75 enrolled subjects participated in other clinical studies during the safety follow up period and none of the subjects experienced any AE during the safety follow up period. The sponsor was well aware of these co-enrollments and did not instruct the CI to document the other IP used as concomitant medications. The CI has notified the other clinical studies' sponsors for the subjects co-enrolled. Additional procedures have been added to prevent this from happening again in the future. The CI's response is acceptable.

Other items discussed were:

1. Study OPP-002: Subject #(b) (6)'s (low dose OC-01 0.12 mg/mL arm) study eye was documented as the left eye per source record but was listed as the right eye in the eCRF and the submission.
2. Study OPP-101: A protocol deviation reported timely by the site but was not in the sponsor submitted data listings. Subject #(b) (6)'s (OC-01 1.2 mg/mL arm) and #(b) (6)'s (OC-01 0.6 mg/mL arm) IP kits were dispensed incorrectly at Visit 3, although this was immediately correctly with no subject used the wrong kit.

In general, this clinical site appeared to be in compliance with Good Clinical Practice (GCP) except the observations noted above. These observations appear unlikely to have significant impacts on the overall efficacy and safety results.

2. Blair Boehmer, M.D., Site 81 for Study OPP-002 and Site 49 for Study OPP-101
10300 N. Illinois Street, Suite 1020
Indianapolis, IN 46290

This CI was inspected on 08/31-09/03/2021 as a data audit for Studies OPP-002 and OPP-101. This was the first inspection for Dr. Boehmer. The final inspection report is pending at the present time. The following is the summary of the preliminary inspection findings.

For Study ONSET-1 (OPP-002), the study site screened a total of 95 subjects, enrolled 63 subjects, with all 63 subjects completed the study. All source records of 16 of the 63 enrolled subjects were reviewed.

For Study ONSET-2 (OPP-101), the study site screened a total of 72 subjects, enrolled 40 subjects, with all 72 subjects completed the study. All source records of 10 of the 40 enrolled subjects were reviewed.

Source records reviewed during the inspection included study protocol and amendments, ICFs, documentation of eligibility criteria and enrollment logs, medical records (including monitoring logs, visits data, laboratory tests, AEs, concomitant medication use), IP accountability records, paper CRFs with eCRFs entries and EDC signature process, protocol deviations, records retention and related regulatory documents (e.g., IRB approvals and communications, staff training logs, ClinicalTrials.gov registration, financial disclosures and delegation of authority).

The inspection found adequate source documentation for the inspected study subjects, with no significant deficiencies reported. The submitted data were verifiable with source records at the study site. The primary efficacy data source was verified. There was no evidence of underreporting of AEs or SAEs.

At the end of the inspection, a Form 483 (Inspectional Observations) was not issued. There were no discussion items. Based on the preliminary inspection findings, this clinical site appeared to be in compliance with GCP.

{See appended electronic signature page}

Ling Yang, M.D., Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Min Lu, M.D., M.P.H.
Team Leader
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE: {See appended electronic signature page}

Kassa Ayalew, M.D., M.P.H
Branch Chief
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CC:
Central Doc. Rm.\NDA 213978
DO\Reviewer\Jennifer Harris
DO\CDTL\William Boyd
DO\Division Director\Wiley Chambers
DO\Project Manager\Dheera Semidey
OSI\DCCE\Division Director\Kassa Ayalew
OSI\DCCE\GCPAB\Branch Chief\Kassa Ayalew
OSI\DCCE\GCPAB\Team Leader\Min Lu
OSI\DCCE\GCPAB\Reviewer\Ling Yang
OSI\DCCE\Program Analysts\Yolanda Patague

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

LING YANG
09/13/2021 09:36:53 AM

MIN LU
09/13/2021 09:59:43 AM

KASSA AYALEW
09/13/2021 10:26:41 AM

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

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

Memorandum

Date: September 7, 2021

To: Dheera Semidey, Regulatory Health Project Manager, Division of Regulatory Operations for Specialty Medicine (DROSM)

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

CC: James Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for TRADENAME™ (varenicline) Nasal Spray

NDA: 213978

In response to DROSM's consult request dated February 8, 2021, OPDP has reviewed the proposed product labeling (PI), patient package insert (PPI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for TRADENAME™ (varenicline) Nasal Spray.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DROSM (Dheera Semidey) on August 24, 2021 and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed PPI and IFU were sent under separate cover on September 1, 2021.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by electronic mail from DROSM (Dheera Semidey) on August 24, 2021 and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Carrie Newcomer at (301) 796-1233 or carrie.newcomer@fda.hhs.gov.

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

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CARRIE A NEWCOMER
09/07/2021 03:53:42 PM

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

PATIENT LABELING REVIEW

Date:	September 1, 2021
To:	Dheera Semidey, PharmD, RAC Regulatory Project Manager **Division of Ophthalmology (DO)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
	Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Maria Nguyen, MSHS, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)**
	Carrie Newcomer, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name):	TRADENAME (varenicline)
Dosage Form and Route:	nasal spray
Application Type/Number:	NDA 213978
Applicant:	Oyster Point Pharma, Inc.

1 INTRODUCTION

On December 17, 2020, Oyster Point Pharma, Inc., submitted for the Agency's review New Drug Application (NDA) #213978 TRADENAME (varenicline) nasal spray. The proposed indication for TRADENAME (varenicline) nasal spray is the treatment of signs and symptoms of dry eye disease.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Ophthalmology (DO) on December 23, 2020 and February 8, 2021, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for TRADENAME (varenicline) nasal spray.

2 MATERIAL REVIEWED

- Draft TRADENAME (varenicline) PPI and IFU received on December 17, 2020, revised by the Review Division throughout the review cycle, and received by DMPP on August 25, 2021 and OPDP on August 24, 2021.
- Draft TRADENAME (varenicline) Prescribing Information (PI) received on December 17, 2020, revised by the Review Division throughout the review cycle, and received by DMPP on August 25, 2021 and OPDP on August 24, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%.

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

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible
- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- rearranged information due to conversion of the PI to Physicians Labeling Rule (PLR) format
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that they are free of promotional language

- ensured that the PPI and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MARY E CARROLL
09/01/2021 08:51:08 AM

JAMES S DVORSKY
09/01/2021 08:56:06 AM

LASHAWN M GRIFFITHS
09/01/2021 09:49:40 AM

HUMAN FACTORS STUDY REPORT AND LABELS 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:	August 9, 2021
Requesting Office or Division:	Division of Ophthalmology (DO)
Application Type and Number:	NDA 213978
Product Type:	Combination Product
Drug Constituent Name and Strength	(b) (4) (varenicline) Nasal Spray, (b) (4) per spray
Device Constituent:	Nasal Spray
Rx or OTC:	Rx
Applicant Name:	Oyster Point Pharmaceuticals (Oyster Point)
Submission Date:	12/17/2020
OSE RCM #:	2020-2679
DMEPA Safety Evaluator:	Jason Flint, MBA, PMP
DMEPA Associate Director for Human Factors (Acting):	Lolita White, PharmD
DMEPA Deputy Director:	Irene Z. Chan, PharmD, BCPS

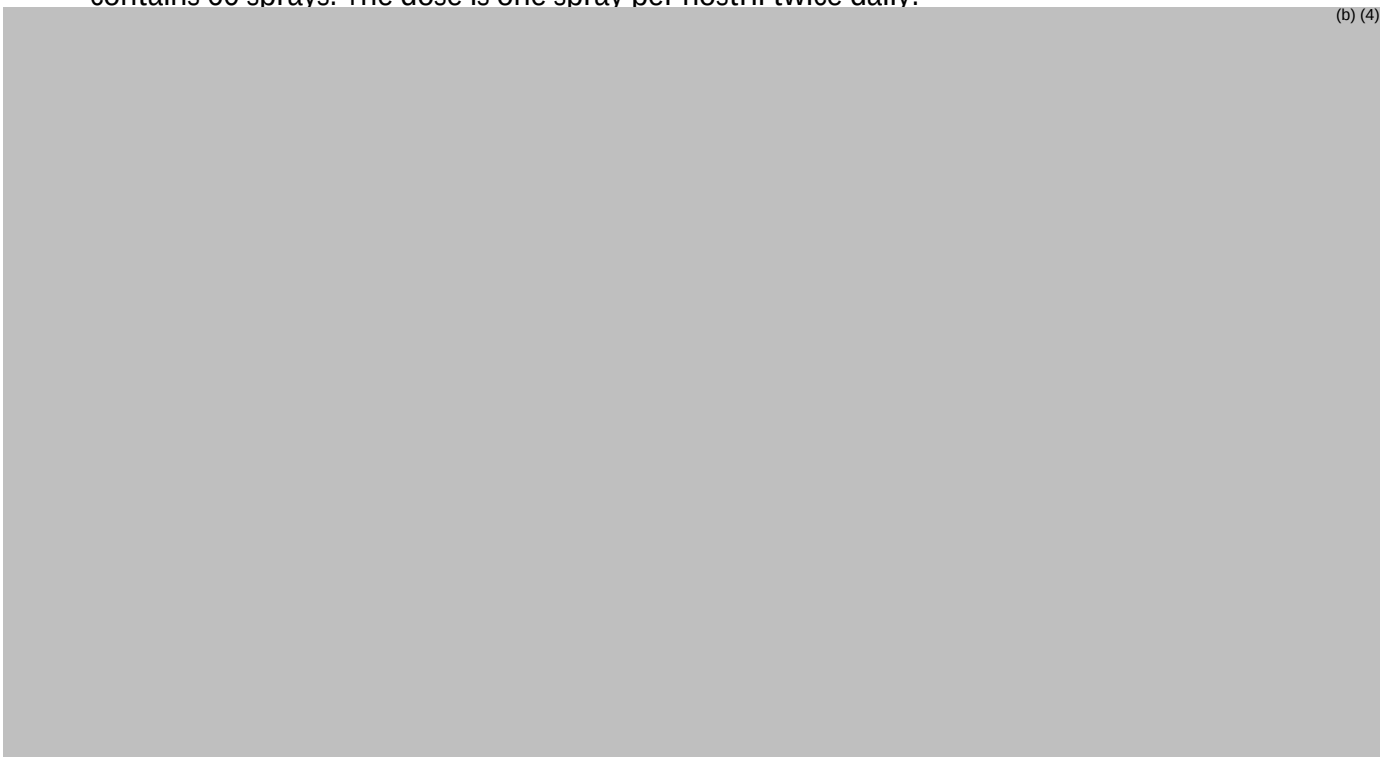
1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report and labels and labeling submitted under NDA 213978 for varenicline nasal spray, (b) (4).

1.1 PRODUCT DESCRIPTION

This is a combination product with a proposed nasal spray device constituent part that is intended to treat the signs and symptoms of dry eye disease. The proposed nasal spray product is intended for use by lay users in the home environment. The product will be packaged in a carton containing two multiple dose nasal spray bottles. Each spray bottle contains 60 sprays. The dose is one spray per nostril twice daily.

(b) (4)



1.2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide our findings and evaluation of each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Report	D

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Information Requests Issued During the Review	E-N/A
Labels and Labeling	F

2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the study design, errors/close calls/use difficulties observed , and our analysis to determine if the results indicate that the user interface is designed to support the safe and effective use of the proposed product.

2.1 SUMMARY OF STUDY DESIGN

Table 2 presents a summary of the HF validation study design. See Appendix C for more details on the study design.

Table 2. Study Methodology for Human Factors (HF) Validation Study	
Study Design Elements	Details
Participants	15 users with a history of dry eye symptoms
Training	No training. Participants were informed that the IFU was available but were not directed to use it.
Test Environment	Simulated home environment
Sequence of Study	• Informed Consent • Study Introduction • Task Completion (simulated use) • Knowledge Tasks • Error debriefing and root cause analysis probing

There was one study deviation due to the COVID-19 pandemic. The task "Gently blow your nose" was not performed to reduce the potential health risk to the moderator and other staff. We find this study deviation to be acceptable in this case.

We do note one methodology concern – participants in the HF validation study were informed that the IFU was available but were not directed to use it. We consider this approach to be leading and prone to bias, however, there were several participants that did not use the IFU during the HF study, so we are not concerned that this may have biased participant responses in this case.

3 RESULTS AND ANALYSES

Table 3 describes the study results, Applicant's analyses of the results, and DMEPA's analyses and recommendations.

Table 3. Identified Issues and DMEPA's Findings		
	Identified Issue and Rationale for Concern	DMEPA's Analysis and Findings
1.	For the task insert nasal applicator into left or right nostril and pump nasal applicator one (1) time per nostril, there were 5 total use errors. Specifically, 5 participants delivered more than one spray into their nostrils. Additionally, for the knowledge task How many sprays are you supposed to administer when using this product?, there were two use errors. The subjective data and the Applicant's root cause analysis stated: Negative transfer of experience with other products and inability to locate information in the IFU. The applicant has not proposed mitigations for these use errors.	If this task is omitted or not performed correctly there is risk of minor site irritation, throat irritation and sneezing. While we acknowledge that negative transfer may have played a role in the observed use errors, that does not mean that the applicant should not have optimized the user interface design to further minimize the residual risk. The root cause analysis indicated that the information in the IFU may not be adequately designed to support performance of this critical task. Based on our overall assessment, we find the IFU can be improved. Our review of the labels and labeling finds that the instruction to deliver 1 spray per nostril in the IFU lacks clarity and prominence. We provide a recommendation in Table 4 to address this concern. We have determined that this change can be implemented without additional HF validation testing to be submitted for review.
2.	For the task Prime the nasal spray device, there were 3 use errors. 3 participants did not prime the nasal spray device. The subjective data and the Applicant's root cause analysis stated: Familiarity with other nasal spray products that do not require priming. The applicant has not proposed mitigations.	If this task is omitted or not performed correctly there is risk of underdose and delayed therapy. While we acknowledge that negative transfer may have played a role in the observed use errors, that does not mean that the applicant should not have optimized the user interface design to further minimize the residual risk. Our review of the study results identified subjective feedback that indicated some participants did not read the IFU because they are familiar with other nasal spray products. This subjective feedback should have been considered by the applicant in

		their analysis regarding further risk reduction strategies that may be warranted. Our expert review of the labels and labeling (user interface, etc.) finds that the priming instruction in the IFU lacks clarity and prominence. Based on our overall assessment, we find the user interface can be improved. We provide recommendations in Table 4 to address this concern. We have determined that this change can be implemented without additional HF validation testing to be submitted for review.
3.	For the task "When inserting the nasal applicator into your nose did you press the tip of it against the inside of your nostril?" there were three use errors. The subjective data and the Applicant's root cause analysis stated: Participants misinterpreted how to aim the product or aimed based on previous experience with other products. We note that the root cause analysis is incomplete for this use error. The applicant has not proposed mitigations for this use error.	Based on the URRA, if this task is omitted or not performed correctly there is risk of underdose. While we acknowledge that negative transfer may have played a role in the observed use errors, that does not mean that the applicant should not have optimized the user interface design to further minimize the residual risk. Our review of the study results identified subjective feedback that indicated that some participants did not read the IFU because they are familiar with other nasal spray products. This subjective feedback should have been considered by the applicant in their analysis regarding further risk reduction strategies that may be warranted. Our expert review of the labels and labeling (user interface, etc.) finds that the instruction in the IFU lacks clarity and prominence. Based on our overall assessment, we find the user interface can be improved. We provide recommendation in Table 4 to address this concern. We have determined that this change can be implemented without additional HF validation testing to be submitted for review.

3.1 ANALYSIS OF OTHER TASK ERRORS

In addition to the critical tasks evaluated in further detail above, the HF validation study showed use errors, (e.g., failures, difficulties, and close calls) with the following five non-critical tasks and 3 non-critical knowledge tasks. We reviewed the available participants' subjective feedback, the Applicant's root cause analysis and Applicant's proposed risk mitigation strategy to determine acceptability of residual risk. Subsequently, we determined the residual risks for the following non-critical tasks is acceptable without further need for risk mitigation strategies:

- Did participant read IFU (not required, for informational purposes only)
- Test participant removes cap and safety clip from OC-01, but do not discard
- Test participant holds nasal spray upright and away from face
- Test participant tilts head slightly; but does not lay head flat
- Test participant replaces safety clip (first) and cap (second)
- How would you characterize your breathing while dispensing the dry eye product?
- For how many days is it safe to use this product after first use?

3.2 LABELS AND LABELING

Tables 4 and 5 below include the identified medication error issues with the submitted labels and labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error. These recommendations can be implemented without submission of additional HF validation data.

Table 5: Identified Issues and Recommendations for Applicant (entire table to be conveyed to Applicant)			
	Identified Issue	Rationale for Concern	Recommendation
Instructions for Use (IFU)			
1.	The images in the IFU can be improved.	We note that some users experienced use errors related to priming and indicated in subjective feedback that the IFU may have contributed to the use errors.	We recommend that the text which correlates to the image for step 3 in the "Steps for Priming TRADENAME Before First Use" section of the IFU be improved to make the text "Press 7 times" more prominent.
		We note in your simulated use validation study that some users failed to demonstrate an understanding that they should deliver one spray per nostril and indicated in subjective feedback that the IFU may have contributed to the use errors.	We recommend that the text which correlates to the image for step 6 in the "Steps for Using TRADENAME Nasal Spray After Priming" section of the IFU be improved to make the text more prominent and more consistent with the priming section of the IFU. We recommend changing the statement "1 time" to read "Press 1 time", and to increase the prominence of this text in the IFU.
		We note in your simulated use validation study that some users failed to demonstrate an understanding that they should not touch the nasal spray tip against the inside of their nostrils. Our review of the IFU indicates that the images for this task may have contributed to the use errors.	We recommend that you improve the image that indicates the user should leave a space between the nasal applicator tip and the wall of the nose.
Carton Labeling			

1.	The product has a Medication Guide; however, the Medication Guide statement is omitted from the principal display panel (PDP).	The Medication Guide provides information that is necessary to patients' safe and effective use of the product. Per 21 CFR 208.24(d), the label shall instruct the authorized dispenser to provide a Medication Guide to each patient and shall state how the Medication Guide is provided.	Revise the PDP to include the Medication Guide statement. For example, "Dispense the enclosed Medication Guide to each patient" or "Dispense the accompanying Medication Guide to each patient" or a similar statement, in accordance with 21 CFR 208.24(d).
2.	The carton labeling can be improved.	We note that the carton contains an "Important" section, however, this section may be improved by removing some text and increasing the prominence of important text.	Revise the "Important" section to read: Read Enclosed Patient Information and Instructions for Use for priming, dosing, and re-priming information. Prime before first use. For Intranasal Use (b) (4) (b) (4) Additionally, consider adding "Prime before first use" on the top of the carton, under the statement "! For intranasal use (b) (4) Do not use in eyes."
Carton and Container Labeling			
1.	As currently presented, the format for the expiration date is not defined.	To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use.	FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.

4 CONCLUSION AND RECOMMENDATIONS

Based on the results of the HF validation study, we have determined that certain changes should be implemented in the design of the user interface to further support safe and effective use of the product. These changes can be implemented without additional HF validation testing. Our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 5 for the Applicant. We ask that the Division convey Table 5 in its entirety to the applicant so that recommendations are implemented prior to approval of this NDA.

4.1 RECOMMENDATIONS FOR OYSTER POINT PHARMACEUTICALS

Our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 5 and we recommend that you implement these recommendations prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for varenicline nasal spray that Oyster Point Pharmaceuticals submitted on December 17, 2020.

Table 5. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	Cholinergic agonist
Active Ingredient (Drug or Biologic)	varenicline
Indication	Treatment of signs and symptoms of dry eye disease
Route of Administration	Intranasal
Dosage Form	Nasal spray
Strength	(b) (4) mg/mL
Dose and Frequency	(b) (4) spray in each nostril twice a day
How Supplied	Carton containing two nasal spray bottle
Storage	20°C to 25°C (68°F to 77°F); (b) (4)
Container Closure/Device Constituent	Nasal Spray Bottle
Intended Users	Lay Users
Intended Use Environment	Home use environments

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On May 18, 2021, we searched the L:drive and AIMS using the terms, “varenicline”, “138645” and “213978” to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search did not identify previous reviews.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

The background information can be accessible in the HF results report. See Appendix D.

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:
\\CDSESUB1\evsprod\nda213978\0002\m5\53-clin-stud-rep\535-rep-effic-safety-stud\dry-eye-disease\5354-other-stud-rep\11483-445-01r\11483-445-01r-rev-a.pdf
URRA: \\CDSESUB1\evsprod\nda213978\0017\m5\53-clin-stud-rep\535-rep-effic-safety-stud\dry-eye-disease\5354-other-stud-rep\11483-330-01-rev-a\11483-330-01-rev-a-urra.pdf

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

APPENDIX F. LABELS AND LABELING

E.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[1] along with postmarket medication error data, we reviewed the following varenicline labels and labeling submitted by Oyster Point Pharmaceuticals on December 17, 2020.

Carton and Container	\\CDSESUB1\evsprod\nda213978\0001\m1\us\ (b) (4) trade-60.pdf
Medication Guide and Instructions for Use	\\CDSESUB1\evsprod\nda213978\0001\m1\us\medication-guide.pdf
Prescribing Information	\\CDSESUB1\evsprod\nda213978\0001\m1\us\proposed.pdf

[1] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

E.2 Label and Labeling Images

(b) (4)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JASON A FLINT
08/09/2021 11:40:30 AM

LOLITA G WHITE
08/09/2021 12:34:32 PM

IRENE Z CHAN
08/09/2021 12:52:41 PM