

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**210565Orig1s000**

**OTHER REVIEW(S)**

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

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

## Memorandum

**Date:** August 9, 2018

**To:** Dheera Semidey  
Regulatory Project Manager  
Division of Transplant and Ophthalmology Products (DTOP)

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

**Subject:** **NDA: 210565**  
**INVELTYS™ (loteprednol etabonate ophthalmic suspension)**  
**1%, for topical ophthalmic use**

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OPDP has reviewed the proposed Package Insert (PI) and carton and container labeling submitted for consult on December 21, 2017, for INVELTYS™ (loteprednol etabonate ophthalmic suspension) 1%, for topical ophthalmic use. Our review is based on the version of the proposed PI and carton and container labeling that was emailed to OPDP by DTOP on August 3, 2018. OPDP's comments are provided directly on the attached version of the proposed PI. OPDP's comments on the proposed carton and container labeling (also attached) are provided below.

### **Carton and Container**

1. OPDP is concerned that the prominence and disparate font styles of the established name and proprietary name in the presentations on the carton and container labeling do not meet the regulatory requirements. Therefore, OPDP recommends revising the established name on the proposed carton and container labeling to be in accordance with 21CFR 201.10(g)(2) which states that, "[t]he established name shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features."

2. The placement of the image of the eye within the “V” of INVELTYS represents intervening matter. We recommend that the proprietary name and the established name not be separated by placement of intervening matter that, in any way would detract, obfuscate, or de-emphasize the established name of the product, or obscure the relationship between the proprietary name and the established name. Therefore, OPDP recommends revising accordingly.

Thank you for your consult. If you have any questions on our comments for the proposed labeling, please contact Carrie Newcomer at 6-1233, or [carrie.newcomer@fda.hhs.gov](mailto:carrie.newcomer@fda.hhs.gov).

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

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CARRIE A NEWCOMER  
08/09/2018

### Clinical Inspection Summary

|                                  |                                                                                                                                                                                                |
|----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Date</b>                      | June 12, 2018                                                                                                                                                                                  |
| <b>From</b>                      | Roy Blay, Ph.D., Reviewer<br>Good Clinical Practice Assessment Branch<br>Division of Clinical Compliance Evaluation<br>Office of Scientific Investigations (OSI)                               |
| <b>To</b>                        | William Boyd, M.D., Clinical Team Leader<br>Martin Nevitt, M.D., Clinical Reviewer<br>Dheera Semiday, Regulatory Project Manager<br>Division of Transplantation and Ophthalmic Products (DTOP) |
| <b>NDA#</b>                      | 210565                                                                                                                                                                                         |
| <b>Applicant</b>                 | Kala Pharmaceuticals, Inc.                                                                                                                                                                     |
| <b>Drug</b>                      | INVELTYS (loteprednol etabonate ophthalmic suspension) 1%                                                                                                                                      |
| <b>NME</b>                       | No                                                                                                                                                                                             |
| <b>Review Priority</b>           | Standard                                                                                                                                                                                       |
| <b>Proposed Indication</b>       | Treatment of post-operative inflammation and pain following ocular surgery                                                                                                                     |
| <b>Consultation Request Date</b> | December 13, 2017                                                                                                                                                                              |
| <b>Summary Goal Date</b>         | June 15, 2018                                                                                                                                                                                  |
| <b>Action Goal Date</b>          | July 1, 2018                                                                                                                                                                                   |
| <b>PDUFA Date</b>                | August 24, 2018                                                                                                                                                                                |

#### 1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Martel and Milstein were inspected in support of this NDA. Based on the results of these inspections, the studies appear to have been conducted adequately, and the data generated by these sites appear acceptable in support of the respective indication. The final classification of the inspections of Drs. Martel and Milstein was No Action Indicated (NAI).

#### 2. BACKGROUND

The Applicant submitted this NDA to support the use of INVELTYS (loteprednol etabonate ophthalmic suspension) 1% for the treatment of post-operative inflammation and pain following ocular surgery.

Inspections were requested for the following protocols in support of this application:

**Protocol KPI-121-C-001**, “A Phase 3, Double-Masked, Randomized, Controlled Trial of KPI-121 in Postsurgical Inflammation”

**Protocol KPI-121-C-005**, “A Phase 3, Double-Masked, Randomized, Controlled Study to Evaluate the Safety and Efficacy of KPI-121 1% Ophthalmic Suspension in Subjects with Postsurgical Inflammation and Pain”

Protocol KPI-121-C-001

This study was conducted at 24 study sites in the U.S. randomizing 380 subjects.

The primary objective of this study was to evaluate the efficacy and safety of KPI-121 ophthalmic suspension compared to placebo in subjects who experience inflammation following cataract surgery.

The primary efficacy endpoints were evaluated using hierarchical statistical testing in the following sequence:

1. the difference in the proportion of study eyes with complete resolution of anterior chamber cells (grade = 0) at postoperative Day 8 maintained through end of study and no need for rescue medication for KPI-121 0.25% QID compared to placebo
2. the difference in the proportion of study eyes with complete resolution of anterior chamber cells (grade = 0) at postoperative Day 8 maintained through end of study and no need for rescue medication for KPI-121 1.0% BID compared to placebo
3. the difference in the proportion of study eyes with complete resolution of pain (grade= 0) at postoperative Day 8 maintained through end of study and no need for rescue medication for KPI-121 1.0% BID compared to placebo
4. the difference in the proportion of study eyes with complete resolution of pain (grade= 0) at postoperative Day 8 maintained through end of study and no need for rescue medication for KPI-121 0.25% QID compared to placebo.

Protocol KPI-121-C-005

This study was conducted at 35 sites in the U.S. randomizing 520 subjects.

The primary objective of this study was to evaluate the efficacy and safety of KPI-121 1% ophthalmic suspension compared to placebo in subjects who have undergone cataract surgery.

The primary endpoints were evaluated using hierarchical statistical testing in the following sequence:

1. The difference in the proportion of study eyes with complete resolution of anterior chamber cells (grade = 0) at postoperative Day 8 maintained through Day 15 without receiving rescue medication prior to Day 15 for KPI-121 1% compared with vehicle
2. The difference in the proportion of study eyes with complete resolution of ocular pain (grade= 0) at postoperative Day 8 maintained through Day 15 without receiving rescue medication prior to Day 15 for KPI-121 1% compared with vehicle

**Rationale for Site Selection**

The clinical sites of Drs. Martel and Milstein were selected for inspection because of their relatively large enrollments and lack of previous inspections.

**3. RESULTS (by site):**

| <b>Site #/<br/>Name of CI/<br/>Address</b>                                                                                                                                                      | <b>Protocol #/<br/># of Subjects<br/>(enrolled)</b> | <b>Inspection Dates</b> | <b>Classification</b> |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|-------------------------|-----------------------|
| Site #112<br><br><b>Bernard Milstein, M.D.</b><br>The Eye Clinic of Texas<br>Affiliate of Houston Eye Associates<br>1100 Gulf Freeway, Suite 114<br>League City, TX 77573<br>Ph: (281) 332-3937 | KPI-121-C-001<br>Subjects: 36                       | 6-19 March 2018         | NAI                   |
| Site #111<br><br><b>Joseph R. Martel, M.D.</b><br>Martel Eye Group<br>11216 Trinity River Drive<br>Rancho Cordova, CA 95670<br>Ph: (916) 635-6161                                               | KPI-121-C-005<br>Subjects: 44                       | 3-5 April 2018          | NAI                   |

Key to Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

**1. Bernard Milstein, M.D.**

At this site for Protocol KPI-121-C-001, 48 subjects were screened, 36 were enrolled, and 35 subjects completed the study. The IRB approved all protocols, amendments, and the informed consent form prior to implementation of any study activities. All subjects signed and dated the consent forms prior to any study-related procedures.

The study records of 30 subjects were reviewed. Source data were compared against data listings. Records reviewed included, but were not limited to, study records, financial report forms, training records, sponsor, monitor, and IRB correspondence, IRB approvals, inclusion/exclusion criteria, randomization logs, patient histories, surgery reports, lab results, concomitant medications, progress notes, and drug accountability and storage.

The primary and secondary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events.

Discussion items included the lack of assessment of AEs for Subjects (b) (6) who reported itchy eyes three days after the start of treatment with the study drug. Dr. Milstein stated that these were normal surgical outcomes and per the protocol did not need to be reported.

## **2. Joseph R. Martel, M.D.**

At this site for Protocol KPI-121-C-005, 52 subjects were screened and 44 subjects were enrolled, all of whom completed the study. The IRB approved all protocols, amendments, and the informed consent form prior to implementation of any study activities. Explicit IRB meeting attendance and voting counts were not present in IRB correspondence at the site. This observation has been referred to the OSI Compliance Oversight Branch for their assessment. The study records of 22 subjects were reviewed; these subjects signed and dated the consent forms prior to any study-related procedures.

Source data were compared against data listings. Records reviewed included, but were not limited to, staff qualifications and training records, financial disclosures, monitoring logs, sponsor, monitor, and IRB correspondence, inclusion/exclusion criteria, rescue medication status, protocol deviations, and drug accountability and storage.

The primary and secondary efficacy endpoint data were verifiable. There was no evidence of underreporting of adverse events.

*{See appended electronic signature page}*

Roy Blay, Ph.D.  
Good Clinical Practice Assessment Branch  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

Phillip Kronstein, M.D.  
Team Leader  
Good Clinical Practice Assessment Branch  
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Office of Scientific Investigations

CONCURRENCE:

*{See appended electronic signature page}*

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

cc:

Central Doc. Rm.\NDA 210565  
DTOP\Division Director\ Renata Albrecht  
DTOP\Team Leader\William Boyd  
DTOP\Medical Officer\Martin Nevitt  
DTOP\Project Manager\Dheera Semiday  
OS\DCCE\Division Director\Ni Khin  
OS\DCCE\GCPAB\Branch Chief\Kassa Ayalew  
OS\DCCE\GCPAB\Team Leader\Phillip Kronstein  
OS\DCCE\GCPAB\Reviewer\Roy Blay  
OS\DCCE\Program Analyst\Yolanda Patague  
OS\Database Project Manager\Dana Walters

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/s/  
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ROY A BLAY  
06/12/2018

PHILLIP D KRONSTEIN  
06/12/2018

SUSAN D THOMPSON  
06/12/2018

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## **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\*\*\***

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|                                       |                                                            |
|---------------------------------------|------------------------------------------------------------|
| <b>Date of This Review:</b>           | May 2, 2018                                                |
| <b>Requesting Office or Division:</b> | Division of Transplant and Ophthalmology Products (DTOP)   |
| <b>Application Type and Number:</b>   | NDA 210565                                                 |
| <b>Product Name and Strength:</b>     | Inveltys (loteprednol etabonate) ophthalmic suspension, 1% |
| <b>Product Type:</b>                  | Single ingredient product                                  |
| <b>Rx or OTC:</b>                     | Rx                                                         |
| <b>Applicant/Sponsor Name:</b>        | Kala Pharmaceuticals, Inc.                                 |
| <b>Submission Date:</b>               | October 24, 2017                                           |
| <b>OSE RCM #:</b>                     | 2017-2280                                                  |
| <b>DMEPA Safety Evaluator:</b>        | Nasim Roosta, PharmD                                       |
| <b>DMEPA Team Leader:</b>             | Otto L. Townsend PharmD                                    |

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## REASON FOR REVIEW

As part of the approval process for Inveltys (loteprednol etabonate) ophthalmic suspension, 1%, the Division of Transplant and Ophthalmology (DTOP) requested that we review the proposed label and labeling for areas that may lead to medication errors.

Kala Pharmaceuticals, Inc. submitted NDA 210565 to seek marketing approval of Inveltys (loteprednol etabonate) ophthalmic suspension, 1% indicated for the treatment of post-operative inflammation and pain following ocular surgery.

## 1 BACKGROUND/REGULATORY HISTORY (IF APPLICABLE) MATERIALS REVIEWED

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

N/A=not applicable for this review

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

## 2 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below includes the identified medication error issues with the submitted label and labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

| Prescribing Information      |                                                                                       |                                                                                                  |                                                                                                                  |
|------------------------------|---------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|
|                              | IDENTIFIED ISSUE                                                                      | RATIONALE FOR CONCERN                                                                            | RECOMMENDATION                                                                                                   |
| Full Prescribing Information |                                                                                       |                                                                                                  |                                                                                                                  |
| 1.                           | In Section 16, the lower numerals of the temperature storage range do not contain the | It is important to label all temperature ranges so that the product can be stored appropriately. | Add C after the number 15° within the Celsius/Centigrade temperature range and add F after the number 59° within |

|  |                                                                   |  |                                                                              |
|--|-------------------------------------------------------------------|--|------------------------------------------------------------------------------|
|  | corresponding abbreviation for Celsius/Centigrade and Fahrenheit. |  | the Fahrenheit temperature range.<br><br>For example:<br>“15° C” and “59° F” |
|--|-------------------------------------------------------------------|--|------------------------------------------------------------------------------|

**Table 3: Identified Issues and Recommendations for Kala Pharmaceuticals (entire table to be conveyed to Applicant)**

| <b>Container Labels</b> |                                                                                               |                                                                                                                                                                |                                                                                                                                                                                                                                                                                 |
|-------------------------|-----------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                         | <b>IDENTIFIED ISSUE</b>                                                                       | <b>RATIONALE FOR CONCERN</b>                                                                                                                                   | <b>RECOMMENDATION</b>                                                                                                                                                                                                                                                           |
| 1.                      | The trade container label for the 2.8 mL bottle is missing the linear barcode.                | The linear barcode is an important safety feature necessary to correctly identify the product and to help prevent product selection and administration errors. | Per 21 CFR 201.25, the linear barcode must appear on the drug’s label (as defined by section 201(k) of the FD&C Act (21 U.S.C. 321(k)), which includes both the carton as well as the container. Thus, there needs to be a linear barcode on both the carton and the container. |
| 2.                      | Expiration date for both 1.2 mL sample bottle and 2.8 mL trade bottle as expressed as MMYYYY. | If the expiration date is not clearly expressed, users can be confused and use expired product (administration errors). <sup>a</sup>                           | Please ensure that the expiration date format is expressed as numbers only. We also recommend that a hyphen or a space be used to separate the month and year portions of the expiration date.                                                                                  |
| <b>Carton Labeling</b>  |                                                                                               |                                                                                                                                                                |                                                                                                                                                                                                                                                                                 |
| 1.                      | The 2.8 mL trade bottle carton labeling is missing the linear barcode.                        | The linear barcode is an important safety feature necessary to correctly identify the product and to help prevent product selection and administration errors. | Per 21 CFR 201.25, the linear barcode must appear on the drug’s label (as defined by section 201(k) of the FD&C Act (21 U.S.C. 321(k)), which includes both the carton as well as the container. Thus,                                                                          |

<sup>a</sup> Draft Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. Food and Drug Administration. 2013. Available from <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf>

|    |                                                                                            |                                                                                                                                                |                                                                                     |
|----|--------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
|    |                                                                                            |                                                                                                                                                | there needs to be a linear barcode on both the carton and the container.            |
| 2. | Both the trade and sample carton labeling includes the statement, "Shake for 1-2 seconds." | When numeric ranges are presented with a dash, users can overlook the dash. The statement, 1-2 seconds, could be misinterpreted as 12 seconds. | Revise the statement, "Shake for 1-2 seconds." to read, "Shake for 1 to 2 seconds." |

### 3 CONCLUSION

DMEPA's evaluation of the proposed label and labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 2 above and ask that the Division conveys the entire table to Kala Pharmaceuticals, Inc. so that recommendations are implemented prior to approval of this NDA.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Inveltys that Kala Pharmaceuticals, Inc. submitted on October 24, 2017.

| <b>Table 4. Relevant Product Information for Inveltys (loteprednol etabonate) 1%</b> |                                                                                                                                                                                   |
|--------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Initial Approval Date</b>                                                         | N/A                                                                                                                                                                               |
| <b>Active Ingredient</b>                                                             | Loteprednol etabonate                                                                                                                                                             |
| <b>Indication</b>                                                                    | Indicated for the treatment of post-operative inflammation and pain following ocular surgery.                                                                                     |
| <b>Route of Administration</b>                                                       | Ophthalmic                                                                                                                                                                        |
| <b>Dosage Form</b>                                                                   | Ophthalmic suspension                                                                                                                                                             |
| <b>Strength</b>                                                                      | 1%                                                                                                                                                                                |
| <b>Dose and Frequency</b>                                                            | Instill one to two drops of Inveltys™ into the affected eye twice daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period. |
| <b>How Supplied</b>                                                                  | 2.8 mL in a 5 mL bottle                                                                                                                                                           |
| <b>Storage</b>                                                                       | Store upright at 15°-25°C (59°-77°F). Do not freeze.                                                                                                                              |

## **APPENDIX B. PREVIOUS DMEPA REVIEWS**

### **B.1 Methods**

On February 1, 2018, we searched the L:drive and AIMS using the terms, Inveltys, to identify reviews previously performed by DMEPA.

### **B.2 Results**

Our search did not identify any results.

## **APPENDIX F. LABELS AND LABELING**

### **F.1 List of Labels and Labeling Reviewed**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>b</sup> along with postmarket medication error data, we reviewed the following Inveltys (loteprednol etabonate) ophthalmic suspension, 1% labels and labeling submitted by Kala Pharmaceuticals on October 24, 2017.

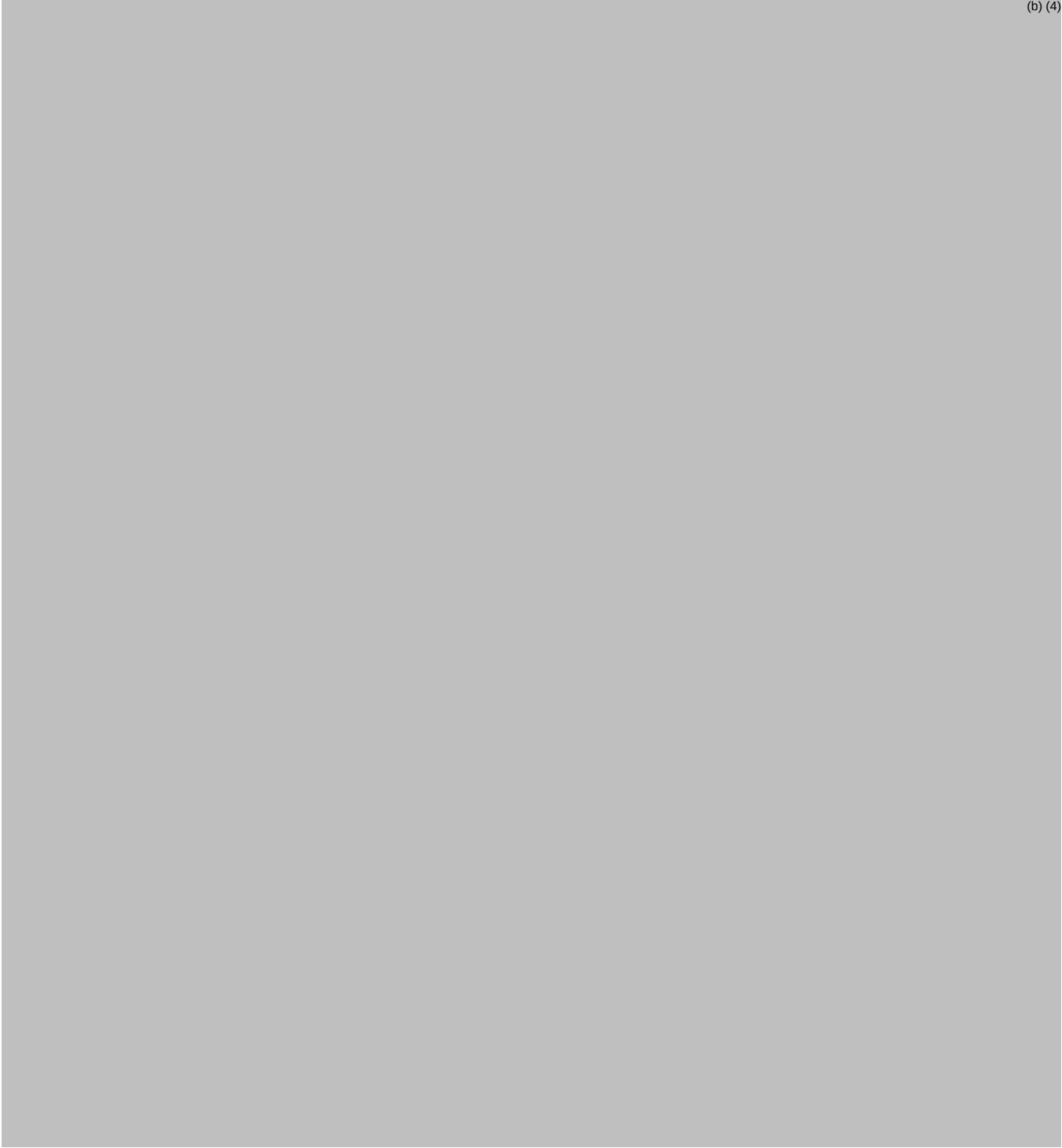
- Container label
- Carton labeling
- Sample Carton Labeling
- Sample container label
- Prescribing Information (Image not shown)

### **F.2 Label and Labeling Images**

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<sup>b</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.





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NASIM N ROOSTA  
05/02/2018

OTTO L TOWNSEND  
05/02/2018