CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208582Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: December 12, 2017

To: Michael Puglisi
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: 208582**
Altafluor Benox (fluorescein sodium and benoxinate hydrochloride ophthalmic solution) 0.25%/0.4% for topical ophthalmic use

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OPDP has reviewed the proposed Carton and Container Labeling submitted for consult on December 11, 2017, for Altafluor Benox (fluorescein sodium and benoxinate hydrochloride ophthalmic solution) 0.25%/0.4% for topical ophthalmic use. OPDP's comment on the proposed carton and container labeling, provided below, is based on the version submitted by the Sponsor to the electronic document room on December 8, 2017, attached.

Carton and Container Label

The proposed labeling includes the following statement (emphasis original):

- "**USUAL DOSAGE**: Instill 1 drop in the eye(s) as needed"

We note that the DOSAGE AND ADMINISTRATION section of the proposed package insert (PI), also submitted by the Sponsor to the electronic document room on December 8, 2017, states, (b) (4) OPDP recommends revising the carton and container labeling to be consistent with the final language in the approved PI.

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

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

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/s/

CARRIE A NEWCOMER
12/12/2017

LABEL AND LABELING REVIEW

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

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

Date of This Review:	October 6, 2017
Requesting Office or Division:	Division of Transplant and Ophthalmology Products (DTOP)
Application Type and Number:	NDA 208582
Product Name and Strength:	(b) (4) (fluorescein sodium and benoxinate hydrochloride) ophthalmic solution, 0.25%/0.4%
Product Type:	Multi-Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Altaire Pharmaceuticals, Inc.
Submission Date:	June 28, 2017 and August 11, 2017
OSE RCM #:	2017-1625
DMEPA Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA Team Leader:	Sarah K. Vee, PharmD

(b) (4)

1 REASON FOR REVIEW

The Division of Transplant and Ophthalmology Products (DTOP) requested we review the proposed container label, carton labeling, and Prescribing Information (PI) for (b) (4) (fluorescein sodium and benoxinate hydrochloride) (NDA 208582), submitted by Altaire Pharmaceuticals, Inc. on August 11, 2017, to determine if it is acceptable from a medication error perspective. The proposed product has been on the market as an unapproved product under the proprietary name, (b) (4) since 2000. DMEPA previously reviewed the label and labeling on in RCM 2016-167 dated June 1, 2016. [c] However, NDA 208582 received a complete response (CR) on June 22, 2016, due to Drug Master File and facilities deficiencies. Thus, the applicant responded to the CR on June 28, 2017 and revised label and labeling on June 28, 2017 and August 11, 2017.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review

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

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

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

We reviewed proposed container label, carton labeling, and Prescribing Information (PI) to determine whether there are any significant concerns in terms of safety related to preventable medication errors. We note that the container label and carton labeling can be improved to enhance the readability and prominence of important information (e.g. route of administration). We also note that the National Drug Code (NDC) numbers, on both the container label and carton labeling, is currently denoted by placeholders. The PI could also be

(b) (4)

improved to facilitate identification of the product. Therefore, we provide recommendations in Section 4.1 for the Applicant to address these concerns.

4 CONCLUSION & RECOMMENDATIONS

We note that the container label and carton labeling can be improved to enhance the readability and prominence of important information (e.g. strength, route of administration). The PI could also be improved to facilitate identification of the product.

4.1 RECOMMENDATIONS FOR ALTAIRE PHARMACEUTICALS, INC.

We recommend the following be implemented prior to approval of this NDA 208582:

A. Container Label, Carton Labeling, Prescribing Information
    a. We note that your NDA has not been granted a proprietary name. Once you receive correspondence from the Agency granting a proprietary name to your NDA, revise all container labels and carton labeling to replace (b) (4) with the new name. Make sure that the established name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2).

B. Container Label
    a. As currently presented, the National Drug Code (NDC) number is denoted by a placeholder (XXXXX-XXX-XX). We request that you add the intended numbers to the container label in accordance with 21 CFR 201.2.

C. Carton Labeling
    a. We recommend relocating the route of administration statement "For Ophthalmic Use" to the principal display panel (PDP) in accordance with 21 CFR 201.100(b)(3), such in the area where the manufacture info is. Move the manufacturer information to the side panel as it clutters the principal display panel and takes readers' attention away from important information such as proprietary and proper names and strength as per Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors, April 2013.
    b. As currently presented, the National Drug Code (NDC) number is denoted by a placeholder (XXXXX-XXX-XX). We request that you add the intended numbers to the carton labeling in accordance with 21 CFR 201.2.

D. Prescribing Information
    a. In the HOW SUPPLIED/STORAGE AND HANDLING section, add the NDC number to facilitate identification in accordance with 21 CFR 201.57(c)(17).

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for fluorescein sodium and benoxinate hydrochloride ophthalmic solution that Altaire Pharmaceuticals, Inc. submitted on June 28, 2017 and August 11, 2017.

Table 2. Relevant Product Information for fluorescein sodium and benoxinate hydrochloride ophthalmic solution	
Initial Approval Date	n/a
Active Ingredient	Fluorescein Sodium and Benoxinate Hydrochloride
Indication	procedures requiring a disclosing agent in combination with a topical ophthalmic anesthetic agent (b) (4) (b) (4)
Route of Administration	Topical Ophthalmic
Dosage Form	Ophthalmic Solution
Strength	0.25%/0.4%
Dose and Frequency	(b) (4)
How Supplied	5 mL glass bottle with a (b) (4) dropper
Storage	Store in refrigerator at 2°-8°C (36°-46°F). Can be stored at room temperature for up to 1 month. Keep tightly closed.
Container Closure	n/a

APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 29, 2017, we searched DMEPA's previous reviews using the terms, fluorescein. Our search identified one previous review[d] and we confirmed that our previous recommendations were implemented or considered.

APPENDIX C. HUMAN FACTORS STUDY – N/A

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On September 27, 2017, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newsletter(s)	Acute Care Community Nursing Long-Term Care Canada Safety Bulletin Pennsylvania Patient Safety Advisory
Search Strategy and Terms	Match Exact Word or Phrase: (b) (4)

D.2 Results

Zero articles were retrieved from the above search.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS) – N/A

APPENDIX F. OTHER – N/A

(b) (4)

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following fluorescein sodium and benoxinate hydrochloride ophthalmic solution labels and labeling submitted by Altaire Pharmaceuticals, Inc. on June 28, 2017 and August 11, 2017.

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

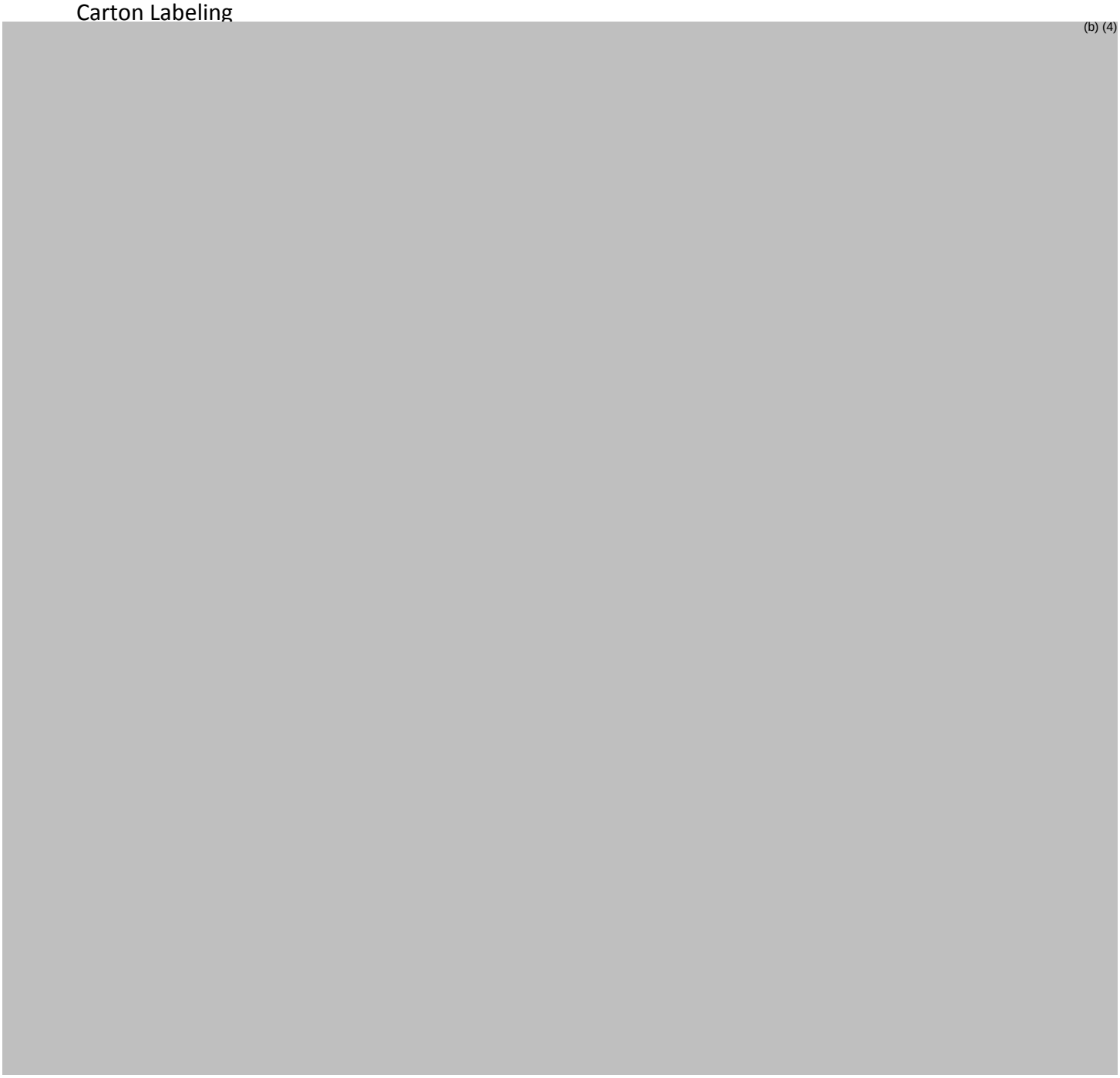
G.2 Label and Labeling Images

(b) (4)

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

Carton Labeling

(b) (4)



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/s/

MADHURI R PATEL
10/06/2017

SARAH K VEE
10/06/2017

Division of Transplant and Ophthalmology Products
Associate Director for Labeling Recommendations
of the Prescribing Information

Product Title	(b) (4) (fluorescein sodium and benoxinate hydrochloride) 0.25%/0.4%
Applicant	Altaire Pharmaceuticals, Inc.
Application/Supplement Number	NDA 208,582
Type of Application/Submission	Original/ Class 2 resubmission
Proposed Indication	For ophthalmic procedures requiring a disclosing agent in combination with anesthetic agent
Date FDA Received Resubmission	June 28, 2017
PDUFA Action Date	December 28, 2017
Review Date	August 22, 2017
Reviewer	Jane Filie, MD
Project Manager	Michael Puglisi

This Associate Director for Labeling (ADL) memorandum provides recommendations for consideration by the management of the Division of Transplant and Ophthalmology Products (DTOP), on the content and format of the prescribing information (PI) to help ensure that the PI:

- Is compliant with Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) requirements[1]
- Is consistent with labeling guidance recommendations[2] and with CDER/OND best labeling practices and policies
- Conveys the essential scientific information needed for safe and effective use of the product
- Is clinically meaningful and scientifically accurate
- Is a useful communication tool for health care providers
- Is consistent with other PI with the same active moiety, drug class, or similar indication

This is a class 2 resubmission after the applicant received a Complete Response Letter (July 21, 2016), due to deficiencies at the manufacturing site. No labeling was agreed upon in the initial cycle.

This combination product, fluorescein sodium 0.25% and benoxinate hydrochloride 0.4% has been marketed in the United States as an ophthalmic solution from several manufacturers,

[1] See *January 2006 Physician Labeling Rule*; 21 CFR 201.56 and 201.57; and *December 2014 Pregnancy and Lactation Labeling Rule* available at https://www.federalregister.gov/documents/2014/12/04/2014-28241/content-and-format-of-labeling-for-human-prescription-drug-and-biological-products-requirements-for

[2] See *PLR Requirements for PI* website for PLR labeling guidances.

without FDA approval. (b) (4) has been in the market since 2005 by the applicant and several other fluorescein sodium 0.25%/ benoxinate hydrochloride 0.4% combination products have been marketed without approval since 1995.

This submission is a literature-based 505(b)(2) application. The applicant has not conducted any clinical safety and efficacy studies, any clinical pharmacology studies or any toxicology studies to support the NDA. Fluorescein sodium has been widely used topically for ophthalmologic purposes since 1882 and there are no approved NDAs for topical use. Nevertheless, fluorescein is marketed as an injectable product for intravenous use, indicated for diagnostic fluorescein angiography or angioscopy of the retina and iris vasculature, approved under NDA 21,980 Fluorescite and NDA 22,186 AK-Fluor. Benoxinate hydrochloride is a topical anesthetic and the 0.4% ophthalmic solution was originally permitted into market in 1953 as NDA 8,729 Dorsacaine, reviewed as part of the Drug Efficacy Study Implementation (DESI).

Labeling Related Consults

I. Medication Error and Proprietary Name Assessments, Division of Medication Error Prevention and Analysis, Office of Surveillance and Epidemiology

The Division of Medication Error Prevention and Analysis (DMEPA) conducted an assessment of the proposed proprietary name and did not find the name vulnerable to confusion that would lead to medication errors and did not consider the name promotional. On 04/21/2016, the proposed proprietary name (b) (4) was conditionally granted.

DMEPA also reviewed the proposed container label, carton labeling, and PI for (b) (4) ophthalmic solution to determine whether there are safety concerns with respect to preventable medication errors. The review team (primary reviewer Michelle Rutledge, PharmD and secondary reviewer Yelena Maslov, PharmD), provided recommendations as follows (for details see review filed on 06/02/2016):

A. Highlights and Full Prescribing Information – Section 2 Dosage and Administration:

(b) (4)

2. Usual Dose to be listed as the subheading in section **2. Dosage and Administration**.

B. Container label and carton labeling

Add the route of administration “For Ophthalmic Use” to the principal display panel.

(b) (4)

II. Office of Prescription Drug Promotion

The Office of Prescription Drug Promotion (OPDP) provided the recommendations on the draft labeling (see memorandum from Meena Ramachandra, PharmD, dated 06/13/2016) as follows:

1. Specification of the “ophthalmic procedures” in **INDICATION AND USAGE**, both in the **HIGHLIGHTS OF PRESCRIBING INFORMATION** and **FULL PRESCRIBING INFORMATION**.
2. Inclusion of incidence rates of adverse reactions if available from the literature references used in support of the application.
3. In section **12 CLINICAL PHARMACOLOGY,** the deletion of the word (b) (4) and instead provide the time to onset of analgesia, which is provided in section 14 of the proposed labeling.

ADL Comment: Recommendation number 1 will be deferred to the clinical team. Recommendation number 2 may not be possible as the information derives from several different literature sources. Recommendation number 3 has been addressed in section **12 CLINICAL PHARMACOLOGY**.

Other Labeling Related Issues

(b) (4)

(b) (4)

Labeling Formatting and Content

Formatting and content recommendations were made with the aim of improving clarity and readability of labeling. The edits and recommendations are shown throughout the proposed labeling in track changes and comments. In the attached PI, the ADL recommendations are presented in track changes throughout the working version of the applicant's draft PI and comments (in balloons) begin with the bolded acronym "ADL".

In order to preserve the comments and track changes, the labeling with track changes may not reflect the final format of the labeling. A clean copy of the entire labeling with my recommendations and suggestions is included in the **APPENDIX.**

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

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/s/

JANE FILIE
09/11/2017

RENATA ALBRECHT
09/11/2017

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # 208582 BLA#	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: ☐ New Indication (SE1) ☐ New Dosing Regimen (SE2) ☐ New Route Of Administration (SE3) ☐ Comparative Efficacy Claim (SE4) ☐ New Patient Population (SE5) ☐ Rx To OTC Switch (SE6) ☐ Accelerated Approval Confirmatory Study (SE7) ☐ Labeling Change With Clinical Data (SE8) ☐ Manufacturing Change With Clinical Data (SE9) ☐ Animal Rule Confirmatory Study (SE10)
Proprietary Name: (b) (4) Established/Proper Name: fluorescein sodium and benoxinate hydrochloride Dosage Form: ophthalmic solution Strengths: 0.25%/0.4%		
Applicant: Altaire Pharmaceuticals, Inc. Agent for Applicant (if applicable):		
Date of Application: December 22, 2015 Date of Receipt: December 22, 2015 Date clock started after Unacceptable for Filing (UN):		
PDUFA/BsUFA Goal Date: June 22, 2016	Action Goal Date (if different):	
Filing Date: February 20, 2016	Date of Filing Meeting: February 2, 2016	
Chemical Classification (original NDAs only) : ☐ Type 1- New Molecular Entity (NME); NME and New Combination ☐ Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination ☐ Type 3- New Dosage Form; New Dosage Form and New Combination ☒ Type 4- New Combination ☐ Type 5- New Formulation or New Manufacturer ☐ Type 7- Drug Already Marketed without Approved NDA ☐ Type 8- Partial Rx to OTC Switch ☐ Type 9-New Indication or Claim (will not be marketed as a separate NDA after approval) ☐ Type 10-New Indication or Claim (will be marketed as a separate NDA after approval)		
Proposed indication(s)/Proposed change(s): for ophthalmic procedures requiring a disclosing agent in combination with anesthetic agent (b) (4) (b) (4)		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:	☐ 505(b)(1) ☒ 505(b)(2) ☐ 505(b)(1) ☐ 505(b)(2)	

Type of BLA ***If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team***	☐ 351(a) ☐ 351(k)
Review Classification: ***The application will be a priority review if:*** • ***A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH)*** • ***The product is a Qualified Infectious Disease Product (QIDP)*** • ***A Tropical Disease Priority Review Voucher was submitted*** • ***A Pediatric Rare Disease Priority Review Voucher was submitted***	☐ Standard ☒ Priority ☐ Pediatric WR ☐ QIDP ☐ Tropical Disease Priority Review Voucher ☐ Pediatric Rare Disease Priority Review Voucher
Resubmission after withdrawal? ☐	Resubmission after refuse to file? ☐
Part 3 Combination Product? ☐ ***If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults***	☐ Convenience kit/Co-package ☐ Pre-filled drug delivery device/system (syringe, patch, etc.) ☐ Pre-filled biologic delivery device/system (syringe, patch, etc.) ☐ Device coated/impregnated/combined with drug ☐ Device coated/impregnated/combined with biologic ☐ Separate products requiring cross-labeling ☐ Drug/Biologic ☐ Possible combination based on cross-labeling of separate products ☐ Other (drug/device/biological product)

☐ Fast Track Designation ☐ Breakthrough Therapy Designation ***(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)*** ☐ Rolling Review ☐ Orphan Designation ☐ Rx-to-OTC switch, Full ☐ Rx-to-OTC switch, Partial ☐ Direct-to-OTC Other:	☐ PMC response ☐ PMR response: ☐ FDAAA [505(o)] ☐ PREA deferred pediatric studies (FDCA Section 505B) ☐ Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) ☐ Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)
Collaborative Review Division (*if OTC product*):	
List referenced IND Number(s): IND 118845	

Goal Dates/Product Names/Classification Properties	**YES**	**NO**	**NA**	**Comment**
PDUFA/BsUFA and Action Goal dates correct in the electronic archive? ***If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.***	☒	☐		
Are the established/proper and applicant names correct in electronic archive? ***If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into electronic***	☒	☐		

archive.				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? ***Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:*** ***http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm*** ***If no, ask the document room staff to make the appropriate entries.***	☒	☐	☐	
Application Integrity Policy	**YES**	**NO**	**NA**	**Comment**
Is the application affected by the Application Integrity Policy (AIP)? ***Check the AIP list at:*** ***http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm***	☐	☒		
If yes, explain in comment column.				
If affected by AIP, has OC been notified of the submission? **If yes,** date notified:	☐	☐		
User Fees	**YES**	**NO**	**NA**	**Comment**
Is Form 3397 (User Fee Cover Sheet)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	☒	☐		

User Fee Status ***If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period from receipt. Review stops. Contact the User Fee Staff. If appropriate, send UN letter.***	Payment for this application *(check daily email from UserFeeAR@fda.hhs.gov):* ☒ Paid ☐ Exempt (orphan, government) ☐ Waived (e.g., small business, public health) ☐ Not required
If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Contact the User Fee Staff. If appropriate, send UN letter.	Payment of other user fees: ☒ Not in arrears ☐ In arrears
User Fee Bundling Policy ***Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:*** ***http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf***	Has the user fee bundling policy been appropriately applied? ***If no, or you are not sure, consult the User Fee Staff.*** ☒ Yes ☐ No

505(b)(2) (NDAs/NDA Efficacy Supplements only)	**YES**	**NO**	**NA**	**Comment**
Is the application a 505(b)(2) NDA? *(Check the 356h form, cover letter, and annotated labeling).* **If yes**, answer the bulleted	☒	☐		

questions below:				
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? **[see 21 CFR 314.54(b)(1)].**	☐	☒		
• Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug **[see 21 CFR 314.54(b)(2)]?** ***If you answered yes to any of the above bulleted questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs for advice.***	☐	☒		
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)? ***Check the Electronic Orange Book at:*** ***http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm*** **If yes**, please list below:	☐	☒		

Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration

If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired orphan or 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.

Exclusivity	**YES**	**NO**	**NA**	**Comment**
Does another product (same active moiety) have orphan exclusivity for the same indication? ***Check the Orphan Drug Designations and Approvals list at:*** ***http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm***	☐	☒		
If another product has orphan exclusivity, is the product considered to be the same product according to the orphan drug definition of sameness **[see 21 CFR 316.3(b)(13)]**? ***If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy***	☐	☐	☒	
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? **If yes**, # years requested: ***Note:*** *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☒	☐	

NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	☐	☒	☐	
If yes, did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? ***If yes, contact the Orange Book Staff (CDER-Orange Book Staff).***	☐	☐	☒	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? ***If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager*** ***Note**: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*	☐	☐	☒	

Format and Content				
Do not check mixed submission if the only electronic component is the content of labeling (COL).	☐ All paper (except for COL) ☒ All electronic ☐ Mixed (paper/electronic) ☐ CTD ☐ Non-CTD ☐ Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission, which parts of the application are submitted in electronic format?				
Overall Format/Content	**YES**	**NO**	**NA**	**Comment**
If electronic submission, does it follow the eCTD guidance?[1] **If not,** explain (e.g., waiver granted).	☒	☐	☐	
Index: Does the submission contain an accurate comprehensive index?	☒	☐		
Is the submission complete as required under 21 CFR 314.50 (*NDAs/NDA efficacy supplements*) or under 21 CFR 601.2 (*BLAs/BLA efficacy supplements*) including: ☒ legible ☒ English (or translated into English)	☒	☐		

[1] http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm333969.pdf

☒ pagination ☒ navigable hyperlinks (electronic submissions only) **If no**, explain.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement? **If yes**, BLA #	☐	☐	☒	

Forms and Certifications
Electronic *forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise,* ***paper*** *forms and certifications with hand-written signatures must be included.* ***Forms*** *include: user fee cover sheet (3397/3792), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674);* ***Certifications*** *include: debarment certification, patent certification(s), field copy certification, and pediatric certification.*

Application Form	**YES**	**NO**	**NA**	**Comment**
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? ***If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].***	☒	☐		
Are all establishments and their registration numbers listed on the form/attached to the form?	☒	☐	☐	
Patent Information (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	☐	☒	☐	
Financial Disclosure	**YES**	**NO**	**NA**	**Comment**
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? ***Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].*** ***Note:*** *Financial disclosure is required for bioequivalence studies that are the basis for approval.*	☐	☒		
Clinical Trials Database	**YES**	**NO**	**NA**	**Comment**
Is form FDA 3674 included with authorized signature? ***If yes, ensure that the application is also coded with the supporting document category, "Form 3674."*** ***If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant***	☒	☐		

Debarment Certification	**YES**	**NO**	**NA**	**Comment**
Is a correctly worded Debarment Certification included with authorized signature? ***Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].*** ***Note:*** *Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e.,"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge…"*	☒	☐	☐	
Field Copy Certification (NDAs/NDA efficacy supplements only)	**YES**	**NO**	**NA**	**Comment**
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? ***Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)*** ***If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.***	☐	☐	☒	
Controlled Substance/Product with Abuse Potential	**YES**	**NO**	**NA**	**Comment**
<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? ***If yes,*** *date consult sent to the Controlled Substance Staff:* <u>For non-NMEs</u>: *Date of consult sent to Controlled Substance Staff* :	☐	☐	☒	
Pediatrics	**YES**	**NO**	**NA**	**Comment**
<u>PREA</u> Does the application trigger PREA? ***If yes, notify PeRC@fda.hhs.gov to schedule required PeRC meeting[2]***	☒	☐		

[2] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027829.htm

***Note**: NDAs/BLAs/efficacy supplements for new active ingredients (including new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.*				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application? ***If no, may be an RTF issue - contact DPMH for advice.***	☒	☐	☐	
BPCA: Is this submission a complete response to a pediatric Written Request? ***If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required[3]***	☐	☒		
Proprietary Name	**YES**	**NO**	**NA**	**Comment**
Is a proposed proprietary name submitted? ***If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."***	☒	☐	☐	
REMS	**YES**	**NO**	**NA**	**Comment**
Is a REMS submitted? ***If yes, send consult to OSE/DRISK and notify OC/ OSI/DSC/PMSB via the CDER OSI RMP mailbox***	☐	☒	☐	
Prescription Labeling	☐ **Not applicable**			
Check all types of labeling submitted.	☒ Package Insert (Prescribing Information)(PI) ☐ Patient Package Insert (PPI) ☐ Instructions for Use (IFU) ☐ Medication Guide (MedGuide) ☒ Carton labeling ☒ Immediate container labels ☐ Diluent labeling ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is Electronic Content of Labeling (COL) submitted in SPL format? ***If no, request applicant to submit SPL before the filing date.***	☒	☐		
Is the PI submitted in Physician Labeling Rule (PLR)	☒	☐		

[3] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/OfficeofNonprescriptionProducts/PediatricandMaternalHealthStaff/ucm027837.htm

format?[4]				
If PI not submitted in PLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.***	☐	☐	☒	
For applications submitted on or after June 30, 2015: Is the PI submitted in Pregnancy and Lactation Labeling Rule (PLLR) format? Has a review of the available pregnancy, lactation, and females and males of reproductive potential data (if applicable) been included?	☒ ☐	☐ ☐	☐ ☒	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR format, was a waiver or deferral requested before the application was received or in the submission? **If requested before application was submitted**, what is the status of the request? ***If no waiver or deferral, request applicant to submit labeling in PLLR format before the filing date.***	☐	☐	☒	
Has all labeling [(PI, patient labeling (PPI, MedGuide, IFU), carton and immediate container labeling)] been consulted to OPDP?	☒	☐	☐	
Has PI and patient labeling (PPI, MedGuide, IFU) been consulted to OSE/DRISK? (*send WORD version if available*)	☐	☐	☒	
Has all labeling [PI, patient labeling (PPI, MedGuide, IFU) carton and immediate container labeling, PI, PPI been consulted/sent to OSE/DMEPA and appropriate CMC review office in OPQ (OBP or ONDP)?	☒	☐	☐	
OTC Labeling	☒ **Not Applicable**			
Check all types of labeling submitted.	☐ Outer carton label ☐ Immediate container label ☐ Blister card ☐ Blister backing label ☐ Consumer Information Leaflet (CIL) ☐ Physician sample ☐ Consumer sample ☐ Other (specify)			
	YES	**NO**	**NA**	**Comment**
Is electronic content of labeling (COL) submitted?	☐	☐		

[4] http://inside fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/LabelingDevelopmentTeam/ucm025576.htm

If no, request in 74-day letter.				
Are annotated specifications submitted for all stock keeping units (SKUs)? ***If no, request in 74-day letter.***	☐	☐	☐	
If representative labeling is submitted, are all represented SKUs defined? ***If no, request in 74-day letter.***	☐	☐	☐	
All labeling/packaging sent to OSE/DMEPA?	☐	☐	☐	
Other Consults	**YES**	**NO**	**NA**	**Comment**
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team) ***If yes, specify consult(s) and date(s) sent:***	☐	☒	☐	
Meeting Minutes/SPAs	**YES**	**NO**	**NA**	**Comment**
End-of Phase 2 meeting(s)? **Date(s):**	☐	☒		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? **Date(s):** 8/26/13, 6/16/15	☒	☐		
Any Special Protocol Assessments (SPAs)? **Date(s):**	☐	X		

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/s/

MICHAEL J PUGLISI
06/22/2016

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

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

Memorandum

Date: June 13, 2016

To: Michael Puglisi, Regulatory Project Manager
Division of Transplant and Ophthalmology Products (DTOP)

From: Meena Ramachandra PharmD, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: (b) (4) (fluorescein sodium and benoxinate hydrochloride ophthalmic solution) 0.25%/0.4% for topical ophthalmic use
NDA 208582

As requested in DTOP's consult dated February 29, 2016, OPDP has reviewed the draft PI for (b) (4) (fluorescein sodium and benoxinate hydrochloride ophthalmic solution) 0.25%/0.4% for topical ophthalmic use.

OPDP reviewed the proposed substantially complete version of the PI titled, "NDA 208582 SCPI.doc" received via e-mail from Michael Puglisi on June 6, 2016. OPDP's comments are provided in the attached clean version of the substantially complete labeling.

Thank you for the opportunity to review and provide comments on this proposed labeling. If you have any questions please contact Meena Ramachandra (240) 402-1348 or Meena.Ramachandra@fda.hhs.gov.

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

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/s/

MEENA RAMACHANDRA
06/13/2016

LABEL AND LABELING REVIEW

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

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

Date of This Review:	June 1, 2016
Requesting Office or Division:	Division of Transplant and Ophthalmology Products (DTOP)
Application Type and Number:	NDA 208582
Product Name and Strength:	(b) (4) (fluorescein sodium and benoxinate hydrochloride solution) 0.25%/0.4% Ophthalmic Solution USP
Product Type:	Multiple Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Altaire Pharmaceuticals, Inc.
Submission Date:	December 22, 2015
OSE RCM #:	2016-167
DMEPA Primary Reviewer:	Michelle Rutledge, PharmD
DMEPA Team Leader:	Yelena Maslov, PharmD

1 REASON FOR REVIEW

The Division of Transplant and Ophthalmology Products (DTOP) requested that we review the (b) (4) (fluorescein sodium and benoxinate hydrochloride solution) 0.25%/0.4% Ophthalmic Solution USP) current container, carton labels, and proposed Prescribing Information for areas that may lead to medication error.

The proposed (b) (4) product has been on the market as an unapproved product under the proprietary name, Altafluor since 2000. It has never been approved by the FDA. On December 22, 2015, Altaire Pharmaceuticals, Inc submitted an NDA for (b) (4) (fluorescein sodium and benoxinate hydrochloride) 0.25%/0.4% and a proposed proprietary name review request for the product on January 27, 2016.

2 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Label and Labeling Review

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

N/A=not applicable for this review
*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

DMEPA evaluated medication errors that occurred with the currently marketed (b) (4) product. Our review identified no relevant cases. See Appendix E for additional details regarding our search.

Additionally, DMEPA reviewed the proposed labels and labeling to determine whether there are significant concerns in terms of safety related to preventable medication errors.

We recommend the proposed label and labeling can be improved to increase prominence of important product information. This, DMEPA will provide its standard recommendation in section 4.

4 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed labels can be improved to increase prominence of important product information and promote the safe use of the product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. **Highlights and Full Prescribing Information – Section 2 Dosage and Administration**:

(b) (4)

2. We recommend Usual Dose be listed as the subheading in Section 2, Dosage and Administration.

4.2 RECOMMENDATIONS FOR ALTAIRE PHARMACEUTICALS, INC.

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

A. Container label and Carton labeling

1. Add the route of administration "For Ophthalmic Use" to the principal display panel.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for [redacted] that Altaire Pharmaceuticals, Inc. submitted on December 22, 2015.

Table 2. Relevant Product Information for [redacted]	
Initial Approval Date	N/A – However, marketed as an unapproved drug since 2000
Active Ingredient	Fluorescein Sodium and Benoxinate Hydrochloride
Indication	[redacted]
Route of Administration	Topical Ophthalmic
Dosage Form	Solution
Strength	0.25%/0.4%
Dose and Frequency	[redacted]
How Supplied	5 mL glass bottle
Storage	Store in refrigerator at 2°-8°C (36°-46°F). Can be stored at room temperature for up to 1 month. Keep tightly closed.
Container Closure	Filled with 5 mL [redacted] glass bottle, with [redacted] cap and [redacted] liner.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On May 31, 2016, we searched the L:drive using the terms, (b) (4) to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified no previous label and labeling reviews.

APPENDIX D. ISMP NEWSLETTERS

D.1 Methods

On May 31, 2016, we searched the Institute for Safe Medication Practices (ISMP) newsletters using the criteria below, and then individually reviewed each newsletter. We limited our analysis to newsletters that described medication errors or actions possibly associated with the label and labeling.

ISMP Newsletters Search Strategy	
ISMP Newletter(s)	Acute Care
Search Strategy and Terms	Match Exact Word or Phrase: (b) (4)

D.2 Results

No articles were identified.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on May 31, 2016 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter.[1]

Table 3: FAERS Search Strategy	
Date Range	May 31, 2016
Product	Fluorescein [active ingredient] benoxinate [active ingredient]
Event (MedDRA Terms)	**DMEPA Official FBIS Search Terms Event List:** Contraindicated Drug Administered (PT) Drug Administered to Patient of Inappropriate Age (PT) Inadequate Aseptic Technique in Use of Product (PT) Medication Errors (HLGT) Overdose (PT) Prescribed Overdose (PT) Prescribed Underdose (PT) Product Adhesion Issue (PT) Product Compounding Quality Issue (PT) Product Formulation Issue (PT) Product Label Issues (HLT) Product Packaging Issues (HLT) Product Use Issue (PT) Underdose (PT)

E.2 Results

Our search retrieved 2 cases, but after further evaluation, we didn't identify any medication error cases that were relevant for this review and could be addressed by labels and labeling revisions.

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

E.4 Description of FAERS

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

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[2] along with postmarket medication error data, we reviewed the following (b) (4) labels and labeling submitted by Altaire Pharmaceuticals, Inc. on December 22, 2015.

- Container label
- Carton labeling
- Prescribing Information (not listed)

G.2 Label and Labeling Images

(b) (4)

[redacted]

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


(b) (4)

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/s/

MICHELLE K RUTLEDGE
06/01/2016

YELENA L MASLOV
06/02/2016