CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206185Orig1s000

OTHER REVIEW(S)

MEMORANDUM

REVIEW OF LABEL AND LABELING

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

Date of This Memorandum:	July 13, 2018
Requesting Office or Division:	Division of Transplant and Ophthalmology (DTOP)
Application Type and Number:	NDA 206185
Product Name and Strength:	Xelpros (Latanoprost) Ophthalmic Emulsion 0.005%
Applicant/Sponsor Name:	Sun Pharma Global FZE
FDA Received Date:	June 7, 2018
OSE RCM #:	2018-962
DMEPA Safety Evaluator:	Nasim Roosta, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 PURPOSE OF MEMORANDUM

The Division of Transplant and Ophthalmology (DTOP) requested that we review the proposed labels and labeling for Xelpros (Appendix A) to determine if they are acceptable from a medication error perspective.

1.1 BACKGROUND

This Application was resubmitted after the Agency issued a Complete Response due to product quality issues. We reviewed the proposed labeling during the previous review cycle and determined the Prescribing Information was acceptable; however, we determined the proposed container labels and carton labeling were unacceptable from a medication error perspective.[a] Since DTOP reserved comment on the proposed labeling until the application was deemed adequate, our recommendations were not conveyed to the Sponsor. Therefore, the labels and labeling submitted for this review cycle on June 7, 2018 are identical to the proposed labels and labeling from the previous review cycle except for the National Drug Codes.

[a] Patel, M. Label and Labeling Review for Xelpros (NDA 206185). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 DEC 13. RCM No.: 2016-2017.

2 CONCLUSION

We agree with our previous findings and provide recommendations in Section 3.

3 RECOMMENDATIONS FOR SUN PHARMA

A. Container Labels (including Professional Sample)

1. The established name lacks prominence compared to the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2). Also, consider increasing the prominence of the established name so that is it readable and so that it is one of the most prominent information on the label per Draft Guidance: Container and Carton, April 2013. Consider choosing a font that is easy to read, and not lightweight or condensed.
2. The strength, expressed as 0.005% next to the established name, lacks prominence. Remove the '125 mcg/2.5 mL' and increase the prominence (i.e., font size) of the 0.005% strength taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.15(a)(6). Also, consider removing the "(b) (4)" that is directly above the statement "For topical use in the eye" as this is repetitive and may allow space for Recommendation A.3.
3. We recommend increasing the prominence of the route of administration statement "For topical use in the eye", as this is critical product information that should be the most prominent information on the Principal Display Panel (PDP) per Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors[b].
4. Currently as presented the professional sample and 1-pack share the same National Drug Code (NDC). We recommend you use a different package code for the professional sample because the NDC is often used for purposes of billing, ordering product, validation during dispensing, and tracking. Having a different package code for the professional sample will help prevent confusion between the professional sample and 1-pack product.

B. Carton Labeling (for 1-pack, 3-pack, and Professional Sample)

1. The established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2). Also, consider increasing the prominence of the established name so that is it readable and so that it is one of

[b] 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

the most prominent information on the label per Draft Guidance: Container and Carton, April 2013[b]. Consider choosing a font that is easy to read, and not lightweight or condensed.

2. The strength, expressed as 0.005% next to the established name, lacks prominence. Remove the '125 mcg/2.5 mL' and increase the prominence (i.e., font size) of the 0.005% strength taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.15(a)(6). Also, consider removing the "(b) (4)%" next to "STERILE" as this is repetitive.
3. We recommend increasing the prominence of the route of administration statement "For topical use in the eye", as this is critical product information that should be the most prominent information on the PDP per Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors[b].
4. To address the risk of patients using opened bottles after (b) (4), revise the Carton Labeling as follows:
   a. Include the statements (b) (4)
   b. Remove the following statement from the 1-pack and professional sample as per the proposed Prescribing Information, it is not applicable to Xelpros: (b) (4)

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

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/s/

NASIM N ROOSTA
07/13/2018

OTTO L TOWNSEND
07/13/2018

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:	December 13, 2016
Requesting Office or Division:	Division of Transplant and Ophthalmology Products (DTOP)
Application Type and Number:	NDA 206185
Product Name and Strength:	Xelpros (Latanoprost) Ophthalmic Emulsion 0.005%
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Sun Pharma Advanced Research Co LTD
Submission Date:	July 28, 2016
OSE RCM #:	2016-2017
DMEPA Primary Reviewer:	Madhuri R. Patel, PharmD.
DMEPA Team Leader:	Mishale Mistry, PharmD., MPH

1 REASON FOR REVIEW

This review evaluates the proposed container label, carton labeling, and Prescribing Information (PI) for Xelpros (latanoprost ophthalmic emulsion) (NDA 206185). Sun Pharma originally submitted label and labeling for Xelpros on April 30, 2014, which DMEPA reviewed.[1] On July 30, 2015, the Division of Transplant and Ophthalmology Products (DTOP) issued a Complete Response (CR) for the application due to deficiencies at the manufacturing facility. Sun Pharma submitted a response to the CR on July 28, 2016 which included new labels and labeling. Subsequently, Division of Transplant and Ophthalmology Products (DTOP) requested that DMEPA review the proposed labels and labeling for areas that may lead to medication errors.

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 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 reviewed the proposed labels and labeling to determine whether there are any significant concerns in terms of safety related to preventable medication errors. DMEPA finds the prescribing information acceptable from a medication error perspective. However, we note that the container label and carton labeling can be improved to enhance the readability and prominence of the established name and product strength. We also note that the the manufacturer logo and graphics are more prominent than other important information on the labels and labeling. Therefore, we provide recommendations in Section 4 for the Applicant to address these concerns.

[1] Kapoor R. Label and Labeling Review for Xelpros NDA 206185. Silver Spring (MD): FDA, CDER, OSE, DMEPA, (US); 2014 Sep 12. RCM No.: 2014-516.

4 CONCLUSION & RECOMMENDATIONS

DMEPA finds the Prescribing Information acceptable from a medication error perspective. However, we note that the proposed container label and carton labeling can be improved to increase the readability and prominence of important information. Please see our letter-ready recommendations in Section 4 below for the container labels and carton labeling.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Carton Labeling
   1. If CMC confirms stability and sterility information of an unopened bottle up to temperatures of 104° F for up to (b) (4), we provide the following recommendations for the Applicant for all Carton Labeling:
      a) Include the statements "(b) (4)
      b) Remove the following statement from the 1-pack and professional sample as per the proposed Prescribing Information, it is not applicable to Xelpros: (b) (4)

4.2 RECOMMENDATIONS FOR SUN PHARMA ADVANCED RESEARCH CO LTD

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

A. Container Labels (including Professional Sample)
   1. The established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2). Also, consider increasing the prominence of the established name so that is it readable and so that it is one of the most prominent information on the label per Draft Guidance: Container and Carton, April 2013. Consider choosing a font that is easy to read, and not lightweight or condensed.
   2. The strength, expressed as 0.005% next to the established name, lacks prominence. Remove the '125 mcg/2.5 mL' and increase the prominence (i.e., font size) of the 0.005% strength taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.15(a)(6). Also, consider removing the "(b) (4)%" that is directly above the statement "For topical use in the eye" as this is repetitive and may allow space for Recommendation A.3.

3. We recommend increasing the prominence of the route of administration statement “For topical use in the eye”, as this is critical product information that should be the most prominent information on the Principal Display Panel (PDP) per Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.
4. Currently as presented the professional sample and 1-pack share the same NDC code. We recommend you use a different package code for the professional sample because the NDC is often used for purposes of billing, ordering product, validation during dispensing, and tracking. Having a different package code for the professional sample will help prevent confusion between the professional sample and 1-pack product.

B. Carton Labeling (for 1-pack, 3-pack, and Professional Sample)

1. The established name lacks prominence commensurate with the proprietary name. Increase the prominence of the established name taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.10(g)(2). Also, consider increasing the prominence of the established name so that is it readable and so that it is one of the most prominent information on the label per Draft Guidance: Container and Carton, April 2013. Consider choosing a font that is easy to read, and not lightweight or condensed.
2. The strength, expressed as 0.005% next to the established name, lacks prominence. Remove the ‘125 mcg/2.5 mL’ and increase the prominence (i.e., font size) of the 0.005% strength taking into account all pertinent factors, including typography, layout, contrast, and other printing features in accordance with 21 CFR 201.15(a)(6). Also, consider removing the “(b) (4)%” next to “STERILE” as this is repetitive.
3. We recommend increasing the prominence of the route of administration statement “For topical use in the eye”, as this is critical product information that should be the most prominent information on the Principal Display Panel (PDP) per Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Xelpros that Sun Pharma Advanced Research Co LTD submitted on July 28, 2016, and the listed drug (LD).

Table 2. Relevant Product Information for Xelpros and the Listed Drug

Product Name	**Xelpros**	**Xalatan**
Initial Approval Date	N/A	6/5/1996
Active Ingredient	Latanoprost	Latanoprost
Indication	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.	Reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.
Route of Administration	Ophthalmic	Ophthalmic
Dosage Form	Ophthalmic Emulsion	Ophthalmic Solution
Strength	0.005%	0.005%
Dose and Frequency	One drop in the affected eye(s) once daily in the evening	One drop in the affected eye(s) once daily in the evening
How Supplied	2.5 mL fill bottle • Package of 1 bottle • Multi-Pack of 3 bottle	2.5 mL fill bottle • Package of 1 bottle • Multi-Pack of 3 bottle
Storage	Store (b) (4) at (b) (4) to 25°C (77°F). May be maintained at temperatures up to 40°C (104°F) for a period not exceeding (b) (4) (b) (4)	Store unopened bottle(s) under refrigeration at 2° to 8°C (36° to 46°F). During shipment to patient, may be maintained at temperatures up to 40°C (104°F) for a period not exceeding 8 days. Once a bottle is opened for use, it may be stored at room temperature up to 25°C (77°F) for 6 weeks.
Container Closure	N/A	N/A

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On October 24, 2016, we searched the L:drive and AIMS using the terms, Xelpros, to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 1 previous label/labeling review, and we confirmed that the one recommendation of changing a statement to "For Topical Use in the Eye" was implemented[2]. The labels/labeling have changed significantly since the last review. We also identified 3 previous proprietary name reviews that are not relevant to this review.

[2] Kapoor, R. Label and Labeling Review for Xelpros (NDA 206185). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2014 SEP 12. RCM No.: 2014-516.

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APPENDIX C. HUMAN FACTORS STUDY – N/A

APPENDIX D. ISMP NEWSLETTERS – N/A

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

APPENDIX F. – N/A

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,[c] along with postmarket medication error data, we reviewed the following Xelpros labels and labeling submitted by Sun Pharma Advanced Research Co LTD on July 28, 2016.

- Container labels
- Carton labeling
- Professional Sample Carton Labeling

G.2 Label and Labeling Images

Container Labels:

(b) (4)

Carton Labeling:

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

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/s/

MADHURI R PATEL
12/13/2016

MISHALE P MISTRY
12/13/2016

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: September 16, 2014

TO: Diana Willard, Regulatory Project Manager
Rhea Lloyd, M.D., Medical Officer
William Boyd, M.D., Medical Team Leader
Division of Transplantation and Ophthalmology Products

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

THROUGH: Janice Pohlman, M.D., M.P.H
Team Leader
Good Clinical Practice Assessment Branch
Division of Good Clinical Practice Compliance
Office of Scientific Investigations

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

SUBJECT: Evaluation of Clinical Inspections

NDA: 206185

APPLICANT: Sun Pharma Advanced Research Company, Ltd. (Sparc)

DRUG: Xelpros (latanoprost ophthalmic (b) (4)) 0.005%

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of open-angle glaucoma or ocular hypertension

CONSULTATION REQUEST DATE:	March 25, 2014
CLINICAL INSPECTION SUMMARY DATE:	September 30, 2014
DIVISION ACTION GOAL DATE:	November 21, 2014
PDUFA DATE:	November 30, 2014

I. BACKGROUND:

The Applicant submitted this NDA to support the use of Xelpros ([(b) (4)] ophthalmic [(b) (4)]) for the treatment of open-angle glaucoma or ocular hypertension.

The pivotal studies, CLR_09_12 entitled "Comparison of the Efficacy and Safety of Sparc's Latanoprost 0.005% Ophthalmic [(b) (4)] (Test) and Xalatan® (Latanoprost 0.005% Ophthalmic Solution - Reference) when Administered Once Daily in Subjects with Open Angle Glaucoma or Ocular Hypertension: a Clinical Non-inferiority Study" and CLR_09_13, entitled "A Clinical Evaluation of Safety of Sparc's Latanoprost 0.005% Ophthalmic [(b) (4)] when Administered Once Daily in Subjects with Open Angle Glaucoma or Ocular Hypertension: an Open Label Extension Study" were inspected in support of the indication.

The clinical sites of Drs. Tepedino, Gira, and Perez were selected for inspection because they were among the highest enrolling sites.

II. RESULTS (by Site):

Name of CI, Location	Protocol #/ Site #/ # of Subjects (enrolled)	Inspection Dates	Final Classification
Michael Tepedino, M.D. Cornerstone Eye Care 1400 E. Hartley Drive High Point, NC 27262-4317	CLR_09_012/ 03/ 43 and CLR_09_013/ 03/ 18	27-30 May 2014	NAI
Joseph Gira, M.D. Ophthalmology Consultants, Ltd. 12990 Manchester Road, Suite 201 St. Louis, MO 63131	CLR_09_013/ 08/ 16	2-4 Jun 2014	NAI
Bernard R. Perez, M.D. International Research Center 4506 Wishart Place Tampa, FL 33603	CLR_09_013/ 13/ 16	2-4 Jun 2014	VAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

1. Michael Tepedino, M.D.
   Cornerstone Eye Care
   1400 E. Hartley Drive
   High Point, NC 27262-4317

a. What was inspected: At this site for Protocol CLR_09_12, 47 subjects were screened, 43 subjects were enrolled, and 41 subjects completed the study. Two subjects discontinued due to adverse events. For Protocol CLR_09_13, 18 subjects were screened and five subjects completed the study. Ten subjects withdrew consent after completing the End of Evaluation study visit, another two withdrew consent during the evaluation period, and one subject was lost to follow up during the evaluation period.

Protocol CLR_09_012

The informed consent forms for all 47 screened subjects were reviewed. The records of 23 of the 43 randomized subjects were reviewed for compliance with inclusion/exclusion criteria and test article accountability. The records of all 43 randomized subjects were reviewed for assessment of the primary efficacy endpoint (intraocular pressure (IOP) measurements) and adverse events. Efficacy and safety endpoint data and adverse events in source documents were compared with line listings. Other records reviewed included firm correspondence and IRB approval.

Protocol CLR_09_013

The informed consent forms for all 18 screened subjects were reviewed. Other records reviewed included adverse events, inclusion/exclusion criteria, safety data, test article accountability, firm correspondence, and IRB approval. Safety data in source documents were compared with line listings.

b. General observations/commentary: A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.

c. Assessment of data integrity: The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

2. Joseph Gira, M.D.
   Ophthalmology Consultants, Ltd.
   12990 Manchester Road, Suite 201
   St. Louis, MO 63131

a. What was inspected: At this site for Protocol CLR_09_013, 16 subjects were screened and enrolled, and 13 subjects completed the study. Two subjects withdrew due to adverse events and one subject withdrew consent. The records of all subjects, screened and/or enrolled, were reviewed. Records included, but were not limited to, informed consent forms, medical histories, laboratory findings, daily diaries, inclusion/exclusion criteria, ocular assessments, primary endpoint data, monitor, contract research organization (CRO), and institutional review board (IRB) communications, electronic case report forms (eCRFs), concomitant medications, and test article storage and accountability. Selected eCRFs were compared with handwritten source documents and with data listings.

b. General observations/commentary: A Form FDA 483 was not issued at the conclusion of the inspection. Review of the records noted above revealed no significant discrepancies or regulatory violations.

c. Assessment of data integrity: The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. Bernard R. Perez, M.D.
International Research Center
4506 Wishart Place
Tampa, FL 33603

a. What was inspected: At this site for Protocol CLR_09_013, 16 subjects were randomized to the study and six subjects completed the study. Eight subjects withdrew consent and two more were terminated early by the sponsor when the study ended. The informed consent forms were reviewed for all study subjects. Other records reviewed included, but were not limited to, IRB and sponsor, and monitor correspondence, adverse events, drug accountability, and concomitant medications. Line listings were compared with source data including intraocular pressures, endothelial cell counts, visual acuity and visual field tests, and dilated ophthalmoscopy and slit lamp biomicroscopy results.

b. General observations/commentary: A Form FDA 483 was issued at the conclusion of the inspection. Review of the records noted above revealed the following:

Observation 1

(a) Subject (b) (6) was hospitalized for a carotid endarterectomy. The site became aware of this hospitalization on March 4, 2011; however, this SAE was not reported until March 21, 2011. Per protocol, SAEs were to be reported to the CRO within one day of awareness of the event.

(b) Subject (b) (6) was discharged from the study after Visit 7 even though the applicable consent form and protocol indicated that this subject should have continued to be seen for Visits 8, 9, and 10.

(c) Subject (b) (6) was discharged from the study after Visit 7 even though the applicable consent form and protocol indicated that this subject should have continued to be seen for Visits 8, 9, and 10.

(d) Subjects (b) (6), and (b) (6) continued in the study without being re-consented with the most recent applicable consent form available.

(e) Subject (b) (6) did not receive an end-of-study visual acuity test as required by protocol.

Observation 2

(a) Subject (b) (6) was hospitalized for a carotid endarterectomy. The site became aware of this hospitalization on March 4, 2011; however, this SAE was not reported until March 21, 2011. Per protocol, SAEs were to be reported to the IRB within three days of awareness of the event.

(b) Subject (b) (6) was hospitalized on (b) (6), for an upper respiratory ailment and sinusitis. The site was made aware of this hospitalization on May 3, 2011; however, the IRB was not notified until June 6, 2011.

Dr. Perez, in his undated written response noted that all of the above observations were documented by the monitor in the subjects' study charts.

With regards to 1(b) Dr. Perez stated that Subject (b) (6) decided not to continue the study on April 29, 2011, and thus did not continue on to Visits 8, 9, and 10.

Dr. Perez committed to corrective actions including increased oversight of studies, formal training for all study coordinators emphasizing SAE reporting and consent procedures, and the inclusion of clarifying language in the study visit source documents as reminders of when re-consenting procedures or SAE reporting would be applicable.

c. **Assessment of data integrity:** Dr. Perez's written response appears adequate. The observations noted above are isolated and would not be expected to adversely affect safety and/or efficacy considerations. The study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical investigator sites of Drs. Tepedino and Gira were not issued Form FDA 483s, and the final classification of these inspections was No Action Indicated (NAI). Dr. Perez's clinical site was issued a Form FDA 483, and the final classification of this inspection was Voluntary Action Indicated (VAI). The data generated by these clinical sites appear adequate in support of the respective indication.

{See appended electronic signature page}

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

CONCURRENCE: *{See appended electronic signature page}*

Janice Pohlman, M.D., M.P.H.
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/s/

ROY A BLAY
09/16/2014

JANICE K POHLMAN
09/16/2014

KASSA AYALEW
09/17/2014

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:	September 12, 2014
Requesting Office or Division:	Division of Transplant and Ophthalmology Products (DTOP)
Application Type and Number:	NDA 206185
Product Name and Strength:	Xelpros (Latanoprost) Ophthalmic Emulsion, 0.005%
Product Type:	Single-Ingredient
Rx or OTC:	Rx
Applicant/Sponsor Name:	Sun Pharmaceutical
Submission Date:	April 30, 2014
OSE RCM #:	2014-516
DMEPA Primary Reviewer:	Rachna Kapoor, PharmD
DMEPA Team Leader:	Yelena Maslov, PharmD

1 REASON FOR REVIEW

This review evaluates the product's design, proposed container label, carton labeling, and prescriber information labeling for Xelpros (Latanoprost) Ophthalmic Emulsion, NDA 206185, for areas of vulnerability that could lead to medication errors.

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
FDA Adverse Event Reporting System (FAERS)	B
Previous DMEPA Reviews	C
Labels and Labeling	D

N/A=not applicable for this review

3 CONCLUSION & RECOMMENDATIONS

DMEPA concludes that the proposed container label, carton labeling and prescriber information can be improved to increase the prominence and readability of important information on the label to promote the safe use of the product.

The color-coding system for the caps and labels for this product are consistent with the American Academy of Ophthalmology recommendation for prostaglandins, which is turquoise.

Based on this review, DMEPA recommends the following be implemented prior to the approval of this NDA:

3.1 RECOMMENDATIONS FOR THE APPLICANT/SPONSOR

A. Container Label
   i. Change the strength expression (b) (4) from '125 mcg/2.5 mL' to '0.005%' and delete the (b) (4)

ii. Consider printing the proprietary name using Title case letter, followed by lower case letters in accordance with the Draft Guidance: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. [1]
iii. Unbold the statement "Rx only".

B. Carton Labeling (package of 1 bottle)
   i. See A.i and A.ii and revise carton labeling accordingly.
   ii. Unbold statements "Rx only" and "One 2.5 mL bottle" on the carton labeling as these statements appear prominent since they are bolded and thus, take attention away from more important information on the labeling such as product's established name, strength and cautionary statements.

C. Carton Labeling (multi-pack of 3 bottles)
   i. See A.i and A.ii and revise carton labeling accordingly.
   ii. Unbold statements "Rx only", "Multi-pack", "Three 2.5 mL bottles" and "Not to be sold separately" on the carton labeling as these statements appear prominent since they are bolded and thus, take attention away from more important information on the labeling such as product's established name, strength and cautionary statements.

D. Prescriber Information
   i. Dangerous abbreviations, symbols, and dose designations that are included on the Institute of Safe Medication Practice's List of Error-Prone Abbreviations, Symbols, and Dose Designations[2] appear in this section of the package insert. As part of a national campaign to avoid the use of dangerous abbreviations and dose designations, FDA agreed not to approve such error prone abbreviations in the approved labeling of products. Thus, please revise those abbreviations, symbols, and dose designations as follows:
      i. Remove the abbreviation 'µg' and replace it with 'mcg' in the Dosage and Administration Section of the prescriber information because the abbreviation 'µg' can be mistaken as 'mg'

[1] 2013 Draft Guidance: *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

[2] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2013 [cited 2014 Sep 8]. Available from: http://www.ismp.org/Tools/errorproneabbreviations.pdf

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Xelpros that Sun Pharmaceuticals submitted on March 5, 2014.

Table 2. Relevant Product Information for Xelpros	
Active Ingredient	Latanoprost
Indication	The reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension
Route of Administration	Ophthalmic
Dosage Form	Ophthalmic emulsion
Strength	0.005%
Dose and Frequency	Instill one drop in the affected eye(s) once daily in the evening
How Supplied	5 mL (b) (4) low density polyethylene bottle (2.5 mL fill volume)
Storage	Store at (b) (4)

APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

B.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on August 6, 2014 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[2]

Table 3: FAERS Search Strategy	
Date Range	**January 1, 2010 to August 1, 2014**
Drug Names	**Latanoprost** [active ingredient]
Event PT	ACCIDENTAL OVERDOSE;CIRCUMSTANCE OR INFORMATION CAPABLE OF LEADING TO MEDICATION ERROR;DRUG ADMINISTRATION ERROR;DRUG DISPENSING ERROR;EXTRA DOSE ADMINISTERED;INAPPROPRIATE SCHEDULE OF DRUG ADMINISTRATION;INCORRECT DOSE ADMINISTERED;INCORRECT DOSE ADMINISTERED BY DEVICE;INCORRECT PRODUCT STORAGE;LABELLED DRUG-DRUG INTERACTION MEDICATION ERROR;MEDICATION ERROR;OVERDOSE;PHYSICAL PRODUCT LABEL ISSUE;PRODUCT DROPPER ISSUE;PRODUCT LABEL CONFUSION;PRODUCT LABEL ISSUE;PRODUCT PACKAGING ISSUE;WRONG TECHNIQUE IN DRUG USAGE PROCESS
Country	**USA**

B.2 Results

Our search identified 196 cases. After individual review, 195 cases were excluded from the final analysis for the following reasons:

- Cases where latanoprost was not the primary suspect (n=7)
- Adverse event not related to a medication error (n=24)
- Product quality issue (n=9)
- Expired medication (n=5)
- Not enough information to analyze case (n=4)

[2] 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.

- Patient discussing drug information with pharmacist or physician (n=2)
- Wrong dose, underdose (not relevant to this review) (n=7)
- Wrong dose, overdose (not relevant to this review) (n=4)
- Bottle of product hard to squeeze (not relevant to this review) (n=9)
- Bottle opening too large, more than one drop falls out (not relevant to this review) (n=38)
- Incorrect product storage (not relevant to this review) (n=13)
- Wrong technique (not relevant to this review) (n=73)

Following exclusions described above, one medication error case remained for our detailed analysis.

- Wrong drug (n=1)
    - The patient in this case stated that she received Xalatan instead of Procardia XL. She mentioned that the pharmacy sent the wrong prescription. Patient was on both medications. Action taken with the suspect drugs and outcomes of the events were unknown. The labels and labeling for Xelpros are clearly differentiated from that for Procardia XL. Additionally, the dosage form for Xelpros is ophthalmic (b) (4) and Procardia XL is extended-release tablets.

B.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the case relevant for this review.

Case Number	Version	Manufacturer Control Number
9241951	2	US-PFIZER INC-2013119137

B.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. Adverse events and medication errors are coded 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 C. PREVIOUS DMEPA REVIEWS

C.1 Methods

We searched the L:Drive Med Err Consults Completed on July 9, 2014 using the term, latanoprost, to identify reviews previously performed by DMEPA.

C.2 Results

A proprietary name review was completed on May 13, 2014 for Xelpros under the same NDA 206185 (OSE RCM#2014-17043).

APPENDIX D. LABELS AND LABELING

D.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[3] along with postmarket medication error data, we reviewed the following Xelpros labels and labeling submitted by Sun Pharmaceutical on July 9, 2014.

- Container Label
- Carton Labeling (package of 1 bottle and multi-pack of 3 bottles)
- Package Insert (no image included)

D.2 Label and Labeling Images

Container Label

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

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

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/s/

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09/12/2014

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