CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211911Orig1s000

OTHER REVIEW(S)

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

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

Memorandum

Date: February 25, 2020

To: Lois Almoza
Regulatory Health Project Manager
Division of Transplant and Ophthalmology Products (DTOP)

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

Subject: **NDA: 211911**
DURYSTA™ (bimatoprost implant), for intracameral administration

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OPDP has reviewed the proposed Package Insert (PI) and Carton and Container Labeling submitted for consult on June 20, 2019, for DURYSTA™ (bimatoprost implant), for intracameral administration (Durysta). Our review is based on the version of the proposed PI located in SharePoint and sent to OPDP via email on February 25, 2020, attached below. OPDP does not have any comments on the proposed PI.

OPDP's comments on the proposed carton and container labeling (also attached) are based on the version located in SharePoint on February 25, 2020 and are provided below.

Carton and Container

1. OPDP recommends that the established name be revised to have prominence commensurate with the proprietary name. The established name should be at least half as large as the letters comprising the proprietary name and the 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, according to 21 CFR 201.10 (g)(2). Please apply this comment to all container and carton labeling.
2. The established name on the carton and container labeling should be consistent with the changes in the PI. Therefore, it should be revised from

"([redacted (b) (4)])" to "(bimatoprost implant)". Please apply this comment to all container and carton labeling.

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.

17 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
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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***

Date of This Review:	January 23, 2020
Requesting Office or Division:	Division of Transplant and Ophthalmology Products (DTOP)
Application Type and Number:	NDA 211911
Product Name and Strength:	Durysta (bimatoprost (b) (4) implant, 10 mcg
Product Type:	Single Ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Allergan
FDA Received Date:	May 6, 2019 and August 28, 2019
OSE RCM #:	2019-1165
DMEPA Safety Evaluator:	Nasim Roosta, PharmD
DMEPA Team Leader:	Otto L. Townsend, PharmD

1 REASON FOR REVIEW

As part of the approval process for Durysta (bimatoprost [redacted] (b) (4) implant, the Division of Transplant and Ophthalmology Products (DTOP) requested that we review the proposed Durysta Prescribing Information (PI), container label, carton labeling and packaging for areas of vulnerability that may lead to medication errors.

2 MATERIALS 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 – N/A
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 or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

Tables 2 and 3 below include the identified medication error issues with the submitted Prescribing Information (PI), container label, carton labeling, packaging, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Transplant and Ophthalmology Products (DTOP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 2 Dosage and Administration			
1.	In Section 2.2, *Administration*, the instructions are presented in paragraph format.	In a written process, numbering the steps in the process may improve readability.	The proposed presentation of the instructions for use without numbered steps may be standard practice for ophthalmology professionals. Therefore, we defer to the clinical team on whether the administration steps should be numbered.

Table 2. Identified Issues and Recommendations for Division of Transplant and Ophthalmology Products (DTOP)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	Section 2.2, *Administration*, instructs the user to examine the foil pouch for damage. However, there are no instructions that inform the user what to do if the foil pouch is damaged.	The user could potentially move forward with using a damaged drug product that could result in patient harm.	Consider including instructions that inform the user how to proceed in the event they find a damaged foil pouch.
3.	Section 2.2., *Administration*, includes a figure (i.e., Figure 1) that includes labels for the safety tab and actuator button (i.e., "a)" and "b)"). These labels lack prominence.	Because the labels (i.e., "a)" and "b)") for the safety tab and actuator button lack prominence, they may be overlooked when the user is referring to the instructions for use.	In Figure 1, consider increasing the prominence of the labels for the safety tab and actuator button. This can be accomplished by increasing the size of the font and/or bolding the font. Additionally, the labels could be changed "1a" and "1b" to correspond with what is specified in the instructions for use.

Table 3. Identified Issues and Recommendations for Allergan (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label (Applicator label)			
1.	The format for expiration date is not defined.	Clearly define the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month.

Table 3. Identified Issues and Recommendations for Allergan (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
Carton Labeling			
1.	The format for expiration date is not defined.	Clearly define the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to

Table 3. Identified Issues and Recommendations for Allergan (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			separate the portions of the expiration date.
2.	The carton labeling does not have a 2D data matrix barcode.	A 2D data matrix barcode is used for tracking and tracing purposes.	In September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act.[1] The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance to determine if the product identifier requirements apply to your product's labeling. [1]The draft guidance is available at: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf.
Packaging label (foil pouch labeling)			
1.	The format for expiration date is not defined.	Clearly define the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only

Table 3. Identified Issues and Recommendations for Allergan (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
2.	The foil pouch labeling displays the statement "C*ontains: Each implant contains 10 mcg of bimatoprost in* (b) (4) *drug delivery system (DDS)."*	The header "*Contains"* seems redundant since the word, "Contains" is also mentioned in the description of the contents.	Consider removing the header "C*ontains"* from the foil pouch labeling.

4 CONCLUSION

Our evaluation of the proposed Durysta Prescribing Information (PI), container label, carton labeling and packaging identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Allergan so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Durysta that Allergan submitted on June 3, 2019.

Table 4. Relevant Product Information for Durysta	
Initial Approval Date	N/A
Active Ingredient	bimatoprost
Indication	Reduction of intraocular pressure in patients with ocular hypertension or open-angle glaucoma
Route of Administration	ophthalmic (intracameral)
Dosage Form	intracameral implant; preloaded in a Novadur drug delivery system
Strength	10 mcg
Dose and Frequency	1 implant (b) (4) into anterior chamber of the affected eye
How Supplied	Single-use applicator with implant pre-loaded that is packaged in an aluminum foil pouch.
Storage	Store refrigerated 2°C - 8°C (36°F - 46°F)

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,[a] along with postmarket medication error data, we reviewed the following Durysta labels and labeling submitted by Allergan.

- Container label
- Carton labeling (trade and professional sample)
- Packaging labeling (trade and professional sample)
- Prescribing Information (Image not shown)

F.2 Label and Labeling Images

Container label (applicator label):

(b) (4)

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

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Clinical Inspection Summary

Date	December 13, 2019
From	Roy Blay, Ph.D., Reviewer Min Lu, M.D., M.P. H., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Willliam Boyd, M.D., Team Leader Martin Nevitt, M.D., Medical Officer Lois Almoza/Judit Milstein., Regulatory Project Managers Division of Transplant and Ophthalmology Products (DTOP)
NDA#	211911
Applicant	Allergan Inc.
Drug	Durysta (bimatoprost intracameral implant, Bimatoprost SR [Sustained Release])
NME	No
Review Priority	Standard
Proposed Indication	The reduction of intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT)
Consultation Request Date	June 18, 2019
Summary Goal Date	December 5, 2019, extended to December 31, 2019
Action Goal Date	February 5, 2020
PDUFA Date	March 5, 2020

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Two clinical investigators, Drs. Evans and Bergstrom, were inspected in support of this NDA. Based on the results of these inspections, the studies (Protocols 192024-091 and 192024-092) appear to have been conducted adequately, and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indication.

An inspection summary addendum will be generated if conclusions change upon receipt and review of the pending Establishment Inspection Reports (EIR) for Dr. Evans's site.

II. BACKGROUND

The Applicant submitted this NDA to support the use of Durysta for the reduction of intraocular pressure (IOP) in patients with open angle glaucoma (OAG) or ocular hypertension (OHT).

Clinical inspections were requested for the following identical protocols (other than projected subject enrollments) in support of this application:

Protocols 192024-091 and 192024-092

Title: "The Efficacy and Safety of Bimatoprost SR in Patients with Open-angle Glaucoma or Ocular Hypertension"

The primary objective of the studies was to evaluate the intraocular pressure (IOP)-lowering efficacy and safety of two dose strengths of Bimatoprost SR in patients with open-angle glaucoma (OAG) or ocular hypertension (OHT) after initial and repeated administrations.

These studies were multicenter, randomized, parallel-group, patient- and efficacy evaluator masked, 20-month evaluations (52-week active treatment period with 8 months extended follow-up) of the safety and efficacy of Bimatoprost SR compared to timolol twice daily in patients with OAG or OHT.

Subjects were randomized to the three treatment groups of Bimatoprost SR 10 µg, Bimatoprost SR 15 µg, or Timolol (control) in a 1:1:1 ratio. Bimatoprost SR-treated subjects received intracameral administration of Bimatoprost SR in the study eye using a prefilled applicator. The blinding was maintained by using vehicle eye drops and/or a sham needleless procedure; i.e., sham administration of the study article.

The primary efficacy endpoint for the study in the U.S. was the study eye IOP as measured using a Goldmann applanation tonometer at each hour evaluated (Hours 0 and 2) at Weeks 2, 6, and 12.

Rationale for Site Selection

The clinical sites of Drs. Evans and Bergstrom were selected for inspection because of their relatively high subject enrollments and lack of recent inspections.

III. RESULTS (by site):

1. **Site #10026**
   Richard Evans, M.D.
   Medical Center Ophthalmology Assoc.
   9157 Huebner Road
   San Antonio, TX 78240
   Dates of inspection: August 12-19, 2019

At this study site, 114 subjects were screened, 29 subjects were enrolled, and 27 subjects completed the study.

Review of the informed consent forms for all 114 screened subjects indicated that informed consent was obtained appropriately prior to the initiation of any study-related procedures. The review of 29 subject records indicated that there was no evidence of under-reporting of adverse events other than a single instance of photophobia for Subject (b) (6) that was not recorded as part of the electronic data capture but was in the source documents.

Other records reviewed for the 29 subjects included, but were not limited to, IRB, sponsor, and monitoring correspondence, financial disclosure forms, training and delegation logs, electronic case report forms (eCRFs) and associated audit trails, the primary efficacy endpoint, and test article accountability and storage conditions.

A Form FDA 483 was issued at the conclusion of the inspection noting that the investigation was not conducted in accordance with the investigational plan and the failure to prepare or maintain adequate case histories.

Three of 29 subjects did not meet inclusion criteria for the selected, randomized eye.

Subject #	OS qualified?	OD qualified	Eye randomized:	Treatment:
(b) (6)	No	Yes	OS	Bimatoprost SR 15 ug
	No	Yes	OS	Bimatoprost SR 10 ug
	Yes	No	OD	Timolol

The left eyes of Subjects (b) (6) and (b) (6) did not meet the Angle Related Eligibility inclusion requirement but were designated as the Study Eyes. The right eye of Subject (b) (6) did not meet the specular microscopy/endothelial cell density inclusion requirement but was designated as the Study Eye. Subject (b) (6) continued in the study but chose to withdraw early from the study (withdrawal was not due to adverse events), and Subjects (b) (6) and (b) (6) continued and completed the study.

Reviewer Note: The designation of the incorrect (non-qualifying) eye as the study eye may affect safety and/or efficacy assessments. The Review Division may wish to consider further assessment of the data from these three subjects given the site's incorrect designation of the study eye.

The FDA Form 483 noted that two of three serious adverse events were not reported within 24 hours of learning of the events as required by protocol.

Subject #	SAE	Date of learning of SAE	Date reporting SAE
(b) (6)	Headache	10 Nov 16	16 Nov 16
	Bradycardia	20 Jan 16	22 Jan 16

The FDA Form 483 also noted the failure to prepare or maintain adequate case histories in that the source documents for determining study eligibility for Subjects (b) (6) and (b) (6) were not available for review. All three subjects were randomized to treatment with Timolol BID.

Reviewer Note: The Review Division may wish to consider a sensitivity analysis of the data from these three subjects given that source data documenting their study eligibility was not available for review.

Verbal discussion with Dr. Evans included observations of storage temperature excursions for ancillary study supplies, and the use of prednisone, a protocol-prohibited medication, for Subject (b) (6) that was documented in the source documents but not in the electronic data capture.

Dr. Evans acknowledged the Form FDA 483 observations and the verbal discussion items and indicated his intention to respond in writing. To date, a written response from Dr. Evans has not been received.

2. Site #10082
Lance Bergstrom, M.D.
Bergstrom Eye and Laser Clinic
2601 South University Drive
Fargo, ND 58103
Dates of inspection: 8/27/19-8/29/19

At this site for Protocol 192024-092, 23 subjects were enrolled, 15 subjects completed the study, six subjects were in follow-up status, and two subjects withdrew from the study.

Review of the informed consent forms for all screened and enrolled subjects indicated that informed consent was obtained appropriately prior to the initiation of any study-related procedures.

Other records reviewed for five subjects included, but were not limited to, training logs, delegation logs, IRB and monitoring communications, financial disclosures, inclusion/exclusion criteria, source documents which were compared with the line listings, subject randomization, laboratory results, the primary efficacy endpoint, concomitant medications, and drug accountability and storage conditions. The primary efficacy endpoint was verifiable, and there was no evidence of under-reporting of adverse events. The site appeared to be in general compliance with GCP.

A Form FDA 483 was not issued as a result of this inspection.

{See appended electronic signature page}

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

CONCURRENCE:

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cc:
Central Doc. Rm.\NDA 211911
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DTOP\CDTL\William Boyd
DTOP\Reviewer\Martin Nevitt
DTOP\Project Managers\Lois Almoza/Judit Milstein
OSI\DCCE\Division Director\Ni Khin
OSI\DCCE\GCPAB\Branch Chief\Kassa Ayalew
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OSI\DCCE\Program Analysts\Yolanda Patague

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/s/

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