CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215092Orig1s000

PRODUCT QUALITY REVIEW(S)

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 215092
Assessment # 2

Drug Product Name	(omidenepag isopropyl) ophthalmic solution
Dosage Form	Ophthalmic solution
Strength	0.002%
Route of Administration	Topical ophthalmic
Rx/OTC Dispensed	Rx
Applicant	Santen, Inc.
US agent, if applicable	

Submission(s) Assessed	Document Date	Discipline(s) Affected
Resubmission	May 6, 2022	All disciplines
Quality Amendment	Jul 20, 2022	Drug product
Quality Amendment	Aug 3, 2022	Facility

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Joseph Leginus	Sithamalli Chandramouli
Drug Product	Milton Sloan	Chunchun Zhang
Manufacturing	Steven Hertz	Yiwei Li
Microbiology	Eric Adeeku	Elizabeth Bearr
Biopharmaceutics	NA	NA
Regulatory Business Process Manager	Kelly Ballard	
Application Technical Lead	Chunchun Zhang	
Laboratory (OTR)	NA	
Environmental	Milton Sloan	Chunchun Zhang

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Adequate	7/14/2021	Reviewed by Monica Cooper
	III			Adequate	8/23/2016	Reviewed by Yushi Feng
	III			Adequate	4/24/2008	Reviewed by George Lunn

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	111518	This product during IND development

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH				
Clinical				
Other				

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Satisfactory information and responses have been submitted to support the drug substance, drug product, quality microbiology and manufacturing process aspects, refer to IQA #1 on 8/28/2021 and each discipline upholds the approval recommendations in the resubmission after reviewing analytical methods transfer and the drug product stability update.

Facilities updates indicated that two FDA inspections NON-RESPONSIVE *at Woodstock Sterile Solutions* (b) (4) *(FEI 1419377). The inspection outcomes confirmed that the previous cited inspection findings had been resolved. The applicant proposed a new testing facility* (b) (4) *for the commercial batch testing functions (release and stability testing). The firm confirmed that* (b) (4) *would not perform commercial testing of the subject product on 8/3/2022. Therefore, OPMA has issued an overall approval recommendation of on Aug 10, 2022. In agreement with the above recommendation, NDA 215092 is recommended approval from Product Quality perspective.*

Labeling recommendations from the Product Quality perspective will be provided to the OND PM for consideration during final labeling discussion.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The drug product omidenepag isopropyl ophthalmic solution, 0.002% is a sterile and preserved solution packaged in 5 mL white low density polyethylene (LDPE) bottle with 2.5 mL fill, a natural linear low density polyethylene (LLDPE) tip, a white high density polyethylene (HDPE) screw cap, and a tamper-evident white LDPE overcap.

Proposed Indication(s) including Intended Patient Population	For the treatment of the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.
Duration of Treatment	Instill one drop in the affected eye(s) once daily in the evening.
Maximum Daily Dose	2 μg/day. As above (see the package insert for details)
Alternative Methods of Administration	NA

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance was referenced to DMF (b) (4). Refer to Dr. Monica Cooper on 7/27/2021. In this resubmission, Dr. Joseph Leginus evaluated two drug substance analytical methods transfer (assay and impurities (related substance)) in (b) (4) and found acceptable on 7/7/2022.

Drug Product: Adequate

Refer to the original drug product review by Dr. Milton Sloan on 8/16/2021.

In this resubmission, the applicant transferred the following drug product analytical methods to the commercial testing site (b) (4). identification, assay of related substances benzalkonium chloride assay, edetate disodium assay. These methods had been validated for release and for the stability studies. The methods transfer studies demonstrated acceptable performance to qualify the site.

Additionally, the applicant has updated three primary stability batches with 36 months stability data when stored at long term storage condition (5°C). The real-time stability studies were conducted in Santen Ltd., Nara, Japan. All the quality attributes met the specifications. Therefore, the expiration date of 36 months is granted when stored at 2°C- 8°C.

The storage statement is (b) (4) and will be finalized at the OND's labeling meeting.

Labeling: Adequate

Labeling recommendations from the Product Quality perspective will be communicated to the OND PM.

Manufacturing: Adequate

Refer to the original OPMA review on 8/15/2021. In the resubmission, the applicant confirmed that (b) (4) is the only release and stability testing site for the commercial batches on 8/3/2022. All the facilities are acceptable. OPMA has issued an overall approval recommendation of on Aug 10, 2022.

Biopharmaceutics: N/A

Microbiology (if applicable): Adequate

Refer to the original microbiology review on 7/27/2021. Dr. Eric Adeeku evaluated USP <71> sterility testing method transfer in (b) (4) and has found adequate on 7/15/2022.

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Sterility	• Formulation • Container closure • Process parameters • Scale/equipment Site	H	(b) (4)	L	Post-approval stability protocol will test sterility.
Assay (API), stability	• Formulation • Container closure • Raw materials	L		L	
Assay (preservative)	• Formulation • Container closure • Process parameters • Scale/equipment	L		L	
Particulate matter	• Formulation • Container closure • Process parameters • Scale/equipment	M		L	
pH	• Formulation • Container closure • Process parameters • Scale/equipment	L		L	

Extractables/ leachables	• Formulation • Container closure	M	(b) (4)	L	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies *(Deficiencies that affect multiple sub-disciplines)*

NA

2. Drug Substance Deficiencies

NA

3. Drug Product Deficiencies

NA

4. Labeling Deficiencies

Communicate to the OND PM

5. Manufacturing Deficiencies

NA

6. Biopharmaceutics Deficiencies

NA

7. Microbiology Deficiencies

NA

8. Other Deficiencies *(Specify discipline, such as Environmental)*

NA

Application Technical Lead Name and Date:

Chunchun Zhang, Ph. D., Aug 10, 2022

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CHAPTER III: ENVIRONMENTAL

IQA NDA Assessment Guide Reference

R REGIONAL INFORMATION

Environmental

ENVIRONMENTAL ASSESSMENT: CLAIM FOR CATEGORICAL EXCLUSION

Santen, Inc. claims that the NDA qualifies for a categorical exclusion in accordance with 21 CFR 25.31(b) and that, to the best of the applicant's knowledge, no extraordinary circumstances exist which may significantly affect the quality of the human environment.

Assessment: ***Remains Adequate***

Primary Environmental Assessor Name and Date:

Milton. J. Sloan, PhD,
Sr. Chemistry Reviewer
OPQ/ONDP/Div3/Branch 6
8/12/2022

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Chunchun Zhang, Ph.D.,
Quality Assessment Lead,
OPQ/ONDP/Div3/Branch 6

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Yes	
Established name(s)	Yes	
Route(s) of administration	Yes	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Yes	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

FULL PRESCRIBING INFORMATION

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	)ophthalmic solution 0.20mg/mL(0.002%)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Yes	
Strength(s) in metric system	Yes	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	N/A	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

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Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Yes	
Dosage form(s) and route(s) of administration	Yes	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Yes	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	Yes	
Pharmacological/ therapeutic class	Yes	
Chemical name, structural formula, molecular weight	Yes	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Yes	

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Yes	
Strength(s) in metric system	Yes	
Available units (e.g., bottles of 100 tablets)	Yes	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yes	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to “Dispense in original container,” provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	(b) (4) DE-117 ophthalmic solution is to be shipped refrigerated. (b) (4) The instructions of “Protected from light” or “Keep in the secondary package carton” are not required for DE-117 ophthalmic solution, based on the photostability test. (b) (4)	
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as “Do not eat.”	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Yes	

Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	
Include information about child-resistant packaging	N/A	

Other Sections of Labeling

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Yes	

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(Copy/paste or refer to a representative example of a proposed container)

3.2 Carton Labeling

(Copy/paste or refer to a representative example of a proposed carton labeling)

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Yes	
Dosage strength	Yes	
Route of administration	Yes	
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	
Net contents (e.g. tablet count)	Yes	
"Rx only" displayed on the principal display	Yes	
NDC number	Yes	
Lot number and expiration date	Yes	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Yes	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Yes	

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Yes	
Medication Guide (if applicable)	Yes	
No text on Ferrule and Cap overseal	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available	N/A	

Assessment of Carton and Container Labeling: ***Adequate***

ITEMS FOR ADDITIONAL ASSESSMENT

N/A

Overall Assessment and Recommendation:

Adequate with revisions. Comments for revision have been added to SharePoint document.

Primary Labeling Assessor Name and Date:
Milton. J. Sloan, PhD,
Sr. Chemistry Reviewer
OPQ/ONDP/Div3/Branch 6

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Chunchun Zhang, Ph.D.,
Quality Assessment Lead,
OPQ/ONDP/Div3/Branch 6

Milton Sloan

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Chunchun Zhang

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M E M O R A N D U M

DATE: July 15, 2022

TO: Chunchun Zhang
Senior Pharm Quality Assessor
CDER/ OPQ/ONDP/DNDPIII/NDPB6

FROM: Eric Adeeku, Ph.D.
Microbiologist
CDER/OPQ/OPMA/DMA1/Branch 1
(240) 402-8571

THROUGH: Elizabeth Bearr, Ph.D.
Senior Pharmaceutical Quality Assessor
CDER/OPQ/OPMA/DMA1/Branch 1

SUBJECT: NDA: 215092
Submission Date: May 06, 2022
Drug Product: Omidenepag isopropyl, 0.002 % (OMLONTI)
Sponsor: Santen Incorporated

The sponsor, Santen Incorporated, resubmitted NDA 215092 on May 6, 2022. As part of the resubmission, the sponsor proposes to add (b) (4) as an alternative analytical testing site for the performance of USP <71> sterility testing. The (b) (4) facility has successfully completed methods transfer to demonstrate their capability to perform the intended testing using the test methods previously submitted in the original application. The experimental design, acceptance criteria applied, and results obtained for a method suitability study performed for the sterility test method as performed by (b) (4) is reviewed below.

(section 3.2.R: Method suitability report-DP-Sterility-(b) (4)).
Test Method: Validation of sterility was performed on one lot (#00618B) of the drug product as per USP <71> Sterility Tests, and (b) (4) Test Procedure, TP00037 (20).
(\\CDSESUB1\evsprod\nda215092\0023\m3\32-body-data\32r-reg-info\method-suitability-rpt-dp-sterility(b) (4).pdf).

Testing was performed in two different sessions, using samples not subjected to the VHP decontamination cycle in the first session and samples that were subjected to the VHP decontamination cycle in the second session.

M E M O R A N D U M

Thirty (30) containers of DE-117 (Omidenepag Isopropyl) Ophthalmic Solution, 0.002 % - 2.5 mL Fill Volume were obtained for each test session.

Method suitability test was performed with 5 bottles of DE-117 (Omidenepag Isopropyl) Ophthalmic Solution, 0.002 % – 2.5 mL per containers per filter. USP <71> states that for ophthalmic preparations wherein the batch is more than 200 containers and the product is 1-40 mL and is not single-dose, 10 containers are adequate to inoculate the 2 media.

After the product filtration three washes each with 100 mL of fluid D were performed. NMT 100 CFU of challenge compendial organisms was inoculated with the third and final wash.

The product positive controls demonstrated growth visually comparable to that of the inoculum controls. No growth was observed in all test negative controls.

Acceptable suitability data was provided for the product lot to demonstrate that the product does not impart bacteriostasis or fungistasis.

Adequate

END

Eric Adeeku

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Elizabeth Bearr

Digitally signed by Elizabeth Bearr
Date: 7/15/2022 03:23:03PM
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/s/

CHUNCHUN N ZHANG
08/10/2022 03:53:03 PM

NDA 215092

Product Quality Assessment (Addendum #2 to Review #1)

From: Chunchun Zhang, SPQA, Branch 6, ONDP/OPQ

Date: Oct 26, 2021

Re: NDA 215092, Omidenepag Isopropyl Ophthalmic Solution, 0.002%

NDA 215092 (Omidenepag Isopropyl Ophthalmic Solution, 0.002 %) was recommended for Complete Response from product quality perspective. Refer to IQA #1 on Aug 18, 2021. The IR and general comments related to the Genus decision from Addendum #1 were communicated to the applicant on 10/15/202. The applicant proposed to discuss the Genus decision comments with the Agency and a meeting is scheduled on 11/1/2021. Additionally, the drug product manufacturing facility, (b) (4) Woodstock Sterile Solutions (FEI 1419377) and the testing facility (b) (4) remain unacceptable. Therefore, NDA 215092 upholds CR recommendation from product quality perspective with one additional comment.

The applicant proposed to withdraw the analytical testing site (b) (4) from the application on 8/31/2021. The agency found the proposal is not acceptable. The following general comment should be included in the CR action letter:

1. *We acknowledge your proposal (dated August 31st, 2021) to withdraw the analytical testing site,* (b) (4) *from the application and commit to a post-approval supplement for a new analytical laboratory. However, your proposal is not acceptable.* (b) (4) *is the only facility listed in the NDA proposed to perform drug product release and stability testing, therefore it is not acceptable to withdraw it without proposing an alternative facility to handle those responsibilities in the application.*

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/s/

CHUNCHUN N ZHANG
10/26/2021 09:41:58 AM

NDA 215092

Product Quality Assessment (Addendum #1 to Review #1)

From: Chunchun Zhang, SPQA, Branch 6, ONDP/OPQ

Date: Oct 8, 2021

Re: NDA 215092, Omidenepag Isopropyl Ophthalmic Solution, 0.002%

NDA 215092 (Omidenepag Isopropyl Ophthalmic Solution, 0.002 %) was recommended for Complete Response from product quality perspective. Refer to IQA #1 on Aug 18, 2021. The drug product has been switched to a drug device combination product because of the Genus decision. However, the device component is a low density polyethylene (LDPE) multi-dose eyedrop bottle and one drop is instilled in the affected eye(s) once daily. A CDRH consult review is not necessary as it is considered as a low risk for a Class 2 combination product based on MAPP 5017.7. Dr. Ashley Boam confirmed that a CDRH QS review/facility consult is not needed on Sep 23, 2021. It is also in agreement with Dr. Wiley Chamber's assessment that no additional review is necessary in the email communication dated Sep 20, 2021. OPPQ recommended to ask the applicant to update 356h form with the device constituent part facilities on Sep 29, 2021. Therefore, NDA 215092 upholds CR recommendation from product quality perspective with the additional IR and comments.

The following IR and general comments should be included in the CR action letter:

IR:

- *Your proposed product is a drug-device combination product. For each submission for this application, indicate that the product is a combination product in field #24 of the FDA Form 356h. Additionally, please refer to the Guidance for Industry, Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER, Questions and Answers, from Oct 2019. For combination products, facilities manufacturing a constituent part of a co-package or single entity combination product, or drug-device combination product that are proposed to be involved in the disposition of commercial product should be included on Form 356h. This includes final kitting facilities and facilities that conduct design control activities, including verification and validation, of a device constituent part.*

General comments:

- *In the Genus decision issued on April 16, 2021, the U.S. Court of Appeals for the District of Columbia Circuit held that articles that meet the device definition in section 201(h) of the FD&C Act must be regulated as devices and not as drugs. In implementing this decision, FDA has determined that the language in 21 CFR 200.50(c) indicating that eye*

cups, eye droppers, and ophthalmic dispensers are regulated as drugs when packaged with other drugs is now obsolete, as these articles meet the "device" definition. FDA will be regulating these products, including your product, as drug-led combination products composed of a drug constituent part that provides the primary mode of action (PMOA) and a device constituent part (an eye cup, dropper, or dispenser). As the drug constituent part provides the PMOA, CDER will have primary jurisdiction over these products, including your product.

- *Combination products are subject to the current good manufacturing practices (CGMP) requirements applicable to each constituent part (drug, device, biological product) of the combination product. However, as reflected in the final rule on CGMPs for combination products (21 CFR part 4), manufacturers have the option to demonstrate compliance both with the drug CGMP regulations (21 CFR parts 210, 211) and with the device quality system (QS) regulation (i.e., 21 CFR part 820) through a streamlined approach. In addition, for combination products that include a biological product constituent part, manufacturers must demonstrate compliance with the CGMP requirements specific to biological products in 21 CFR parts 600 through 680.*

  If utilizing a streamlined approach, you must demonstrate compliance (i) with either the drug CGMP regulations or the QS regulation in their entirety and also (ii) with those provisions specified in part 4 from the other of these two sets of requirements. Alternatively, you may demonstrate compliance with both the drug CGMPs and QS regulation in their entirety (non-streamlined approach). For further information on 21 CFR part 4, see guidance for industry and FDA staff Current Good Manufacturing Practice Requirements for Combination Products (January 2017), available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126198.htm

  Based on an assessment of the risk profile of your proposed combination product, FDA has determined that information to demonstrate compliance with the device QS regulation is most appropriately assessed during inspection, and this information must be available upon inspection to demonstrate your compliance with 21 CFR part 4. Please ensure that the information you have available on-site describes how your firm has implemented each applicable regulation in your manufacturing processes, and that it includes descriptions of the specific procedures and activities conducted by your firm and the protocols used by your firm for each activity.

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/s/

CHUNCHUN N ZHANG
10/08/2021 10:05:20 AM

RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA 215092
Assessment # 1

Drug Product Name	(omidenepag isopropyl) ophthalmic solution
Dosage Form	Ophthalmic solution
Strength	0.002%
Route of Administration	Topical ophthalmic
Rx/OTC Dispensed	Rx
Applicant	Santen, Inc.
US agent, if applicable	

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original	Nov 19, 2020	All disciplines
Quality Amendment	Jan 14, 2021	Facility
Quality Amendment	Feb 22, 2021	Facility
Quality Amendment	Mar 1, 2021	Manufacturing process
Quality Amendment	May 10, 2021	Drug substance, drug product and manufacturing process
Quality Amendment	Jun 3, 2021	Manufacturing process
Quality Amendment	Jul 9, 2021	Manufacturing process
Quality Amendment	Jul 13, 2021	Quality microbiology

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Monica Cooper	Suong Tran
Drug Product	Milton Sloan	Chunchun Zhang
Manufacturing	Steven Hertz	Yiwei Li
Microbiology	Eric Adeeku	Elizabeth Bearr
Biopharmaceutics	NA	NA
Regulatory Business Process Manager	Kelly Ballard	

Application Technical Lead	Chunchun Zhang	
Laboratory (OTR)	NA	
Environmental	Milton Sloan	Chunchun Zhang

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II		(b) (4)	Adequate	7/14/2021	Reviewed by Monica Cooper
	III			Adequate	8/23/2016	Reviewed by Yushi Feng
	III			Adequate	4/24/2008	Reviewed by George Lunn

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
IND	111518	This product during IND development

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH				
Clinical				
Other				

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

Satisfactory information and responses have been submitted to support the drug substance, drug product, quality microbiology and manufacturing process aspects.

The compliance status of the drug product manufacturing facility, (b) (4) *Woodstock Sterile Solutions (FEI 1419377) and testing facility* (b) (4) *were determined unacceptable based on the most recent inspections. Therefore, OPMA has issued an overall recommendation of "Withhold" on Aug 3, 2021. In agreement with the above recommendation, NDA 215092 is recommended Complete Response from Product Quality perspective.*

Labeling recommendations from the Product Quality perspective will be provided to the OND PM for consideration during final labeling discussion.

The following CR statement about the unacceptable manufacturing facilities should be included in the CR letter:

> *During a recent inspection of the* (b) (4) *manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.*
>
> *Following an evaluation of an inspection performed at the* (b) (4) *Woodstock Sterile Solutions (FEI 1419377) manufacturing facility, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the remaining objectionable conditions, and verification by FDA, is required before this application may be approved. We recommend you contact your manufacturing facility if more information is needed.*
>
> *We will continue to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections, once safe travel may resume and based on public health need and other factors.*
>
> *For more information, please see the FDA guidances related to COVID 19. These guidances can be found at https://www.fda.gov/emergency-*

preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The drug product omidenepag isopropyl ophthalmic solution, 0.002% is a sterile and preserved solution packaged in 5 mL white low density polyethylene (LDPE) bottle with 2.5 mL fill, a natural linear low density polyethylene (LLDPE) tip, a white high density polyethylene (HDPE) screw cap, and a tamper-evident white LDPE overcap.

Proposed Indication(s) including Intended Patient Population	For the treatment of the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.
Duration of Treatment	Instill one drop in the affected eye(s) once daily in the evening.
Maximum Daily Dose	2 μg/day. As above (see the package insert for details)
Alternative Methods of Administration	NA

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance, omidenepag isopropyl, is a white to light brown crystal or crystalline powder. Omidenepag isopropyl is manufactured by (b) (4). The chemistry, manufacturing, and controls information for omidenepag isopropyl was referenced to DMF (b) (4) which was recently reviewed and found adequate by Dr. Monica Cooper on 7/14/2021.

Drug Product: Adequate

Omidenepag isopropyl ophthalmic solution, 0.002% is sterile and preserved with 0.005% benzalkonium chloride (BAK). The active ingredient, omidenepag isopropyl, is the pro-drug of its pharmacologically active acid form omidenepag (UR-7276). All the excipients are compendial. The revised drug product specifications are acceptable and include the following quality attributes: description, identification, assay, related substances, benzalkonium chloride assay, edetate disodium assay, osmolality, pH, particulate matter, and sterility. All the analytical methods are adequately validated. Evaluation of the risk assessment of the elemental impurities was performed and indicates the results are lower than the permitted daily exposure (PDE) as noted in USP<232> and ICH Q3D guidance. CoAs for three registration batches including one phase 3

clinical batch; nine clinical batches for US phase 2 and three clinical batches for Japan and Asian countries are provided.

Omidenepag isopropyl ophthalmic solution, 0.002% is packaged in a three-piece container-closure system consisting of a 5-mL white low density polyethylene (LDPE) bottle, a (b) (4) linear low density polyethylene (LLDPE) tip, a (b) (4) high density polyethylene (HDPE) screw cap, and a tamper-evident white LDPE overcap. The container closure system was demonstrated to be suitable for the proposed drug product and cause no safety concerns.

The applicant has submitted three primary stability batches with 24 months stability data when stored at long term storage condition (5°C) and 6 months at accelerated condition (25°C/40%RH). All the quality attributes met the specifications. Extractable/leachable studies were performed and there are no safety concerns for the potential leachables. The drug product is stable to short temperature excursions and not sensitive to light. The in-use stability study indicated that the drug product can be stored at room temperature for one month after opening. Therefore, the expiration date of 30 months is granted when stored at 2°C- 8°C.

The storage statement is (b) (4) and will be finalized at the OND's labeling meeting.

Labeling: Adequate

Labeling recommendations from the Product Quality perspective will be communicated to the OND PM.

Manufacturing: Inadequate

The manufacturing process includes: (b) (4) The applicant adequately responded to all identified process deficiencies. The Overall Manufacturing Inspection Recommendation is to withhold due to the compliance status of (b) (4)

Biopharmaceutics: N/A

Microbiology (if applicable): Adequate

The applicant has provided adequate sterility assurance. The manufacturing process is (b) (4)

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations/ Comments**
Sterility	• Formulation • Container closure • Process parameters • Scale/equipment Site	H	(b) (4)	L	Post-approval stability protocol will test sterility.
Assay (API), stability	• Formulation • Container closure • Raw materials	L		L	
Assay (preservative)	• Formulation • Container closure • Process parameters • Scale/equipment	L		L	
Particulate matter	• Formulation • Container closure • Process parameters • Scale/equipment	M		L	
pH	• Formulation • Container closure • Process parameters • Scale/equipment	L		L	
Extractables/ leachables	• Formulation • Container closure	M		L	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies *(Deficiencies that affect multiple sub-disciplines)*

NA

2. Drug Substance Deficiencies

NA

3. Drug Product Deficiencies

NA

4. Labeling Deficiencies

Communicate to the OND PM

5. Manufacturing Deficiencies

During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

Following an evaluation of an inspection performed at the (b) (4) Woodstock Sterile Solutions (FEI 1419377) manufacturing facility, our field investigator observed objectionable conditions at the facility and conveyed that information to the representative of the facility at the close of the inspection. Satisfactory resolution of the remaining objectionable conditions, and verification by FDA, is required before this application may be approved. We recommend you contact your manufacturing facility if more information is needed.

We will continue to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections, once safe travel may resume and based on public health need and other factors.

For more information, please see the FDA guidances related to COVID 19. These guidances can be found at https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders.

6. Biopharmaceutics Deficiencies

NA

7. Microbiology Deficiencies

NA

8. Other Deficiencies *(Specify discipline, such as Environmental)*

NA

Application Technical Lead Name and Date:

Chunchun Zhang, Ph. D., Aug 18, 2021

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CHAPTER III: ENVIRONMENTAL

IQA NDA Assessment Guide Reference

R REGIONAL INFORMATION

Environmental

ENVIRONMENTAL ASSESSMENT: CLAIM FOR CATEGORICAL EXCLUSION

Santen, Inc. claims that the (b) (4) NDA qualifies for a categorical exclusion in accordance with 21 CFR 25.31(b) and that, to the best of the applicant's knowledge, no extraordinary circumstances exist which may significantly affect the quality of the human environment. The requested categorical exclusion is based on the following estimate of the concentration of omidenepag (active moiety of omidenepag isopropyl) at the point of entry into the aquatic environment. The expected introduction concentration (EIC) of omidenepag was calculated as:

EIC-Aquatic (ppb) = A x B x C x D where

A = kg/year produced for direct use (as active moiety) B = 1/liters per day entering POTWs*

C = year/365 days

D = 10^9 µg/kg (conversion factor)

* 1.214 x 10^{11} liters per day entering publicly owned treatment works (POTWs)

Source: *1996 Needs Survey, Report to Congress.* Information regarding the *Needs Survey* is available on the Internet at http://www.epa.gov/owm.

This calculation assumes:

- All drug product produced in a year are used and enter the publicly owned treatment works (POTW) system
- Drug product usage occurs throughout the United States in proportion to the population and amount of waste water generated.
- There is no metabolism

Based on the above:

If (b) (4) are produced per year (b) (4) kg of omidenepag** would be produced. The expected introduction concentration of omidenepag would then be (b) (4) µg/L, or (b) (4) ppb, which is approximately (b) (4) times less than 1 ppb.

(b) (4)

[redacted] (b) (4)

Thus, less than 1ppb of omidenepag will be released in the aquatic environment (worst case scenario)

[redacted] (b) (4)

Assessment: ***Adequate***

Primary Environmental Assessor Name and Date:

Milton. J. Sloan, PhD,
Sr. Chemistry Reviewer
OPQ/ONDP/Div3/Branch 6
8/12/2021

Secondary Assessor Name and Date (and Secondary Summary, as needed):

Chunchun Zhang, Ph.D.,
Quality Assessment Lead,
OPQ/ONDP/Div3/Branch 6

CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Yes	
Established name(s)	Yes	
Route(s) of administration	Yes	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Yes	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

FULL PRESCRIBING INFORMATION

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	N/A	)ophthalmic solution 0.20mg/mL(0.002%)

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Yes	
Strength(s) in metric system	Yes	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	N/A	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

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Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Yes	
Dosage form(s) and route(s) of administration	Yes	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	N/A	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Yes	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	Yes	
Pharmacological/ therapeutic class	Yes	
Chemical name, structural formula, molecular weight	Yes	
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Yes	

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	N/A	

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Yes	
Strength(s) in metric system	Yes	
Available units (e.g., bottles of 100 tablets)	Yes	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yes	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to “Dispense in original container,” provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	(b) (4) DE-117 ophthalmic solution is to be shipped refrigerated. (b) (4) . The instructions of “Protected from light” or “Keep in the secondary package carton” are not required for DE-117 ophthalmic solution, based on the photostability test. (b) (4)	
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as “Do not eat.”	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Yes	

Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	N/A	
Include information about child-resistant packaging	N/A	

Other Sections of Labeling

(b) (4)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Yes	

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(Copy/paste or refer to a representative example of a proposed container)

3.2 Carton Labeling

(Copy/paste or refer to a representative example of a proposed carton labeling)

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Yes	
Dosage strength	Yes	
Route of administration	Yes	
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	N/A	
Net contents (e.g. tablet count)	Yes	
"Rx only" displayed on the principal display	Yes	
NDC number	Yes	
Lot number and expiration date	Yes	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Yes	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Yes	

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Yes	
Medication Guide (if applicable)	Yes	
No text on Ferrule and Cap overseal	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available	N/A	

Assessment of Carton and Container Labeling: ***Adequate***

ITEMS FOR ADDITIONAL ASSESSMENT

N/A

Overall Assessment and Recommendation:

Adequate with revisions. Comments for revision have been added to SharePoint document.

Primary Labeling Assessor Name and Date:
Milton. J. Sloan, PhD,
Sr. Chemistry Reviewer
OPQ/ONDP/Div3/Branch 6

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Chunchun Zhang, Ph.D.,
Quality Assessment Lead,
OPQ/ONDP/Div3/Branch 6

Milton Sloan

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Chunchun Zhang

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CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	215092
Assessment Cycle Number	01
Drug Product Name/ Strength	DE-117 Ophthalmic Solution / 0.002 %
Route of Administration	Topical ophthalmic
Applicant's Name	Santen Incorporated
Therapeutic Classification/ OND Division	N/A
Manufacturing Site	(b) (4)
Method of Sterilization	

Assessment Recommendation: **Adequate**

Assessment Summary:

The submission is **recommended** for approval.

List Submissions being assessed (table):

Document(s) Assessed	Date Received
1 (eCTD sequence 0001)	11/19/2020
5 (eCTD sequence 0005)	01/14/2021
8 (eCTD sequence 0008)	03/01/2021
11 (eCTD sequence 0011)	03/19/2021
14 (eCTD sequence 0014)	05/10/2021
18 (eCTD sequence 0008)	07/13/2021

List Submissions being assessed:

Submit	Received	Review Request	Assigned to Reviewer
11/19/2020	11/19/2020	N/A	12/01/2020
01/14/2021	01/14/2021	N/A	01/25/2021
03/01/2021	03/01/2021	N/A	03/19/2021
03/19/2021	03/19/2021	N/A	N/A
05/10/2021	05/10/2021	N/A	N/A
07/13/2021	07/13/2021	N/A	07/13/2021

Remarks:

This is an electronic submission.
Goal date is 09/19/2021.

Response to the Agency's 12/21/2020, 02/24/2021 and 07/07/2021 information request letters were provided 01/14/2021, 03/01/2021 and 07/13/2021 respectively. Additional stability data were provided in the 03/19/2021 and 05/10/2021 submissions. The preservative content specification was revised in the 05/10/2021 submission.

Concise Description of Outstanding Issues: No outstanding issues remain.

Supporting Documents:
A207284MR02.docx – Sterility assurance review of product manufactured in the same facility and referenced for BI incubation conditions. Review was recommended for approval on 09/13/2018.

Product Quality Microbiology Assessment

This review contains original information as well as response to microbiology deficiencies conveyed to the sponsor in the Agency's information request letters dated 12/21/2020, 02/24/2021 and 07/07/2021. The most recent deficiencies are italicized.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Description of drug product –

(section 3.2.P.1.1: Description and Composition of the drug product).

The drug product, 0.002 % DE-117 ophthalmic solution, is a sterile aqueous preparation that contains the pharmaceutical ingredient omidenepag isopropyl, 0.02 mg/mL. The drug product is preserved with 0.005 % benzalkonium chloride (BAK) and contains other inactive ingredients as listed below. The drug product is filled in a three-piece multi-dose container closure system described below.

Drug product composition –

(section 3.2.P.1.2: Description and Composition of the drug product).

Ingredient	Function	Quantity (mg/mL)	Quantity / unit (mg)
Omidenepag isopropyl, in house	Active ingredient	0.02	0.05
Sodium citrate, USP	(b) (4)		
Citric acid monohydrate, USP			
Polyoxyl 35 castor oil, NF			
Benzalkonium chloride, NF	Preservative	0.05	0.125
Edetate disodium, USP	(b) (4)		
Glycerin, USP			
Sodium hydroxide, NF / Hydrochloric acid, NF	pH adjuster	q.s. pH (b) (4)	q.s. pH (b) (4)
Water for Injection, USP	(b) (4)		

Description of container closure system –

(section 3.2.P.1.3: Description and Composition of the drug product).

The 0.002 % DE-117 ophthalmic solution, 2.5 mL, is filled in 5-mL low density polyethylene (LDPE) (b) (4) bottles with polyethylene tips, high density polyethylene screw caps and tamper-evident low-density polyethylene overcap.

Component	Description	Manufacturer
Bottle	5-mL low density polyethylene (LDPE) (b) (4) bottles	(b) (4)
Tip	(b) (4) Polyethylene LLDPE tips	
Cap	(b) (4) HDPE caps	

The sponsor provided an adequate description of the drug product composition and the container closure system designed to maintain product sterility.

Adequate

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

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/s/

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