CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022388Orig1s000

PRODUCT QUALITY REVIEW(S)

NDA 022388

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

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

Date: Feb 24, 2022

Re: NDA 022388, Acuvue theravision™ with Ketotifen (etafilcon A lens with ketotifen), 0.019 mg

---

NDA 022388 (Acuvue theravision™ with Ketotifen (etafilcon A lens with ketotifen), 0.019 mg) was recommended pending in IQA #1 on Dec 21, 2021. The Pre-Approval Inspections of Ortec, Inc (FEI: 3004285326) and Johnson & Johnson Ireland (FEI: 3003083595) were conducted and found acceptable. Therefore, the Office of Pharmaceutical Manufacturing Assessment (OPMA) has issued an overall acceptable recommendation for all the facilities on 2/24/2022. All the other disciplines uphold the approval recommendation. In agreement with the above recommendation, NDA 022388 is recommended approval from Product Quality perspective.

66 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHUNCHUN N ZHANG
02/24/2022 02:36:42 PM

RECOMMENDATION

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

NDA 022388
Assessment # 1

Drug Product Name	Acuvue theravision™ with Ketotifen (etafilcon A lens with ketotifen)
Dosage Form	Contact lens
Strength	0.019 mg
Route of Administration	Ocular
Rx/OTC Dispensed	Rx
Applicant	Johnson & Johnson Vision Care, Inc. (JJVC)
US agent, if applicable	

Submission(s) Assessed	Document Date	Discipline(s) Affected
Original	Apr 30, 2021	All disciplines
Quality Amendment	Jun 17, 2021	Facility
Quality Amendment	Jun 25, 2021	Quality microbiology
Quality Amendment	Jul 30, 2021	Facilities
Quality Amendment	Aug 25, 2021	Facilities and manufacturing process
Quality Amendment	Oct 13, 2021	Quality microbiology and manufacturing process
Quality Amendment	Oct 20, 2021	Manufacturing process
Quality Amendment	Nov 1, 2021	Biopharmaceutics
Quality Amendment	Nov 8, 2021	Biopharmaceutics
Quality Amendment	Dec 1, 2021	Drug product, facilities and manufacturing process; quality microbiology

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessor	Secondary Assessor
Drug Substance	Ben Zhang	Suong Tran

Drug Product	Milton Sloan	Chunchun Zhang
Manufacturing	Laurie Nelson	Vidya Pai
Microbiology	Laura Wasil	Christine Craig
Biopharmaceutics	Joan Zhao	Om Anand
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
[redacted]	II	[redacted]	[redacted]	Adequate	9/27/2021	Reviewed by Ben Zhang
	III			NA		
	III			NA		

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

Document	Application Number	Description
IND	66883	This product during IND development

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH		Withhold (evaluating device manufacturing sites)	12/7/2021	Stacey Cecco
Clinical				
Other				

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

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

The Pre-Approval Inspections of Ortec, Inc (FEI: 3004285326) and Johnson & Johnson Ireland (FEI: 3003083595) are currently pending. Therefore, the final OPMA recommendation cannot be provided at this time. Therefore, OPMA has issued an overall recommendation of "pending" on Dec 14, 2021. In agreement with the above recommendation, NDA 022388 is recommended pending 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 proposed product K-Lens is regulated as drug device combination product which includes the drug component (buffered ketotifen fumarate solution (BKS) and device component (etafilcon A soft contact lens). K-Lens is packaged in a blister bowl and a foil laminated lidstock and secondary is a folding carton.

Proposed Indication(s) including Intended Patient Population	For the treatment of correcting refractive ametropia (myopia and hyperopia) in phakic or aphakic patients.
Duration of Treatment	Insert one lens per eye per day
Maximum Daily Dose	0.038 mg/day. As above (see the package insert for details)
Alternative Methods of Administration	NA

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance, Ketotifen Fumarate is a white to brownish-yellow, crystalline powder. All the CMC information is referenced in DMF (b) (4)

which was reviewed and found acceptable by Dr. Ben Zhang on 9/27/2021.

Drug Product: Adequate

K-Lens is composed of an etafilcon A soft hydrophilic contact lens with 0.019 mg of ketotifen. The contact lens is packaged with a buffered ketotifen solution (BKS). All the excipients are compendial.
The revised drug product specifications are acceptable and include the appropriate quality attributes. 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.

K-Lens is stored in a blister bowl with a foil laminated lidstock and then in a folding carton. The container closure system was demonstrated to be suitable for the proposed drug product and cause no safety concerns.

The applicant has submitted stability batches at -12.00D and +6.00D lenses in studies VIS-STB-000243 (12 batches for 24 months), VIS-STB-005405 (2 batches for 24 months), VIS-STB-005346 (9 batches for 9months) at 25°C/40%RH and 6 months at 40°C/25%RH. All the quality attributes met the specifications. Extractable/leachable studies were performed and there are no safety concerns for the potential leachables. Photostability indicated that K-Lens is sensitive to light and should be protected from light. Therefore, the expiration date of 18 months is granted when stored at 15°C- 25°C in the commercial container closure system.

The storage statement is “Store at 15°C-25°C. Protect from light.” 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 drug constituent part manufacturing process consists of (b) (4) (b) (4) The applicant adequately responded to all identified process deficiencies.

All the facilities are acceptable with the exception of the Pre-Approval Inspections of Ortec, Inc/ FEI: 3004285326 and Johnson & Johnson

Ireland/ FEI: 3003083595 are currently pending. Therefore, the final OPMA recommendation cannot be provided at this time.

Biopharmaceutics: Adequate

The proposed quality control dissolution method and acceptance criteria is acceptable. The Applicant has provided sufficient data and justification to support the bridging the K-lens combination product manufactured in JJVC and JJVC-CP.

Microbiology (if applicable): Adequate

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

C. Risk Assessment

I. From Initial Risk Identification			Review Assessment		
Attribute/CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Eval.	Lifecycle Considerations
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	
Uniformity of Dosage unit	Formulation Container closure Process parameters Scale/equipment	M		L	
pH	Formulation Container closure Process parameters Scale/equipment	L		L	
Drug release	Formulation Container closure Process parameters Scale/equipment	M		L	

Drug device performance	Formulation Container closure	H	(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

Pending

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., Dec 21, 2021

68 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

CHAPTER III: ENVIRONMENTAL

IQA NDA Assessment Guide Reference

R REGIONAL INFORMATION

Environmental

Ketotifen fumarate is a FDA approved molecular entity which functions as an H1-antihistamine / mast cell stabilizer. It is currently marketed in the form of ophthalmic solution under the brand name Zaditor® (Novartis), and Alaway® (Bausch and Lomb). The active ingredient for the combination product in this NDA submission (NDA #022388) is ketotifen (formula C19H19NOS, CAS# 34580-14-8, formula weight 425.5 g/mol). The theoretical content of ketotifen in ketotifen fumarate is (b) (4)

The estimated concentration of ketotifen at the point of entry into the aquatic environment will be below 1 part per billion (ppb) and hence does not require the preparation of Environmental Assessment (EA) or Environmental Impact Statement (EIS) [Ref. 21 CFR 25.31(b)]. The estimate of the concentration of ketotifen at the point of entry into the aquatic environment is presented in Attachment 1.1

Johnson & Johnson Vision Care, Inc. (JJVC), Jacksonville, FL, certifies that the above referenced action meets the criteria for a categorical exclusion defined in the regulations (21 CFR 25.31[b]) and that to the knowledge of JJVC, no extraordinary circumstances exist. Thus, no environmental assessment needs to be performed.

Attachment: Estimate of the Concentration of Ketotifen at the Point of Entry into the Aquatic Environment

Assessment: ***Adequate***
The claim of categorical exclusion is acceptable.

Primary Environmental Assessor Name and Date:

Milton. J. Sloan, PhD,
Sr. Chemistry Reviewer
OPQ/ONDP/Div3/Branch 6
12/10/2021

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	
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	

1.2 FULL PRESCRIBING INFORMATION

2. DOSAGE AND ADMINISTRATION

(b) (4)

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

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)	Yes	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

(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	Yes	
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	

3 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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.	Yes	
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.		
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	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

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	

How Supplied

(b) (4)

[redacted]

Storage and Handling

(b) (4)

[redacted]

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.)	Yes	K-Lens should be stored in the original secondary carton to protect from light.
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.	store at 15°C to 25°C	
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	N/A	

natural rubber latex. Avoid statements such as "latex-free."		
Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

(b) (4)

1.2.6 Manufacturing Information After Section 17 (for drug products)

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

(b) (4)

[redacted]

3.2 Carton Labeling

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

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

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	0.019 mg of ketotifen per lens	Recommendation to revise to "19 mcg"
Route of administration		
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	None	Recommendation to revise to "(b) (4) [redacted]
Net contents (e.g. tablet count)	N/A	
"Rx only" displayed on the principal display	None	Recommendation to include "Rx only"
NDC number	None	
Lot number and expiration date	None	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	None	Recommendation to add storage statement Also see DMEPA review consult for same
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/Inadequate}***

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

ITEMS FOR ADDITIONAL ASSESSMENT

Comments added to draft label:

http://sharepoint.fda.gov/orgs/CDER-OND/dtopndas

Overall Assessment and Recommendation:

Comments added to draft label:

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

http://sharepoint.fda.gov/orgs/CDER-OND/dtopndas

Milton Sloan

Digitally signed by Milton Sloan
Date: 12/17/2021 09:56:55AM
GUID: 508da72000029fa0e17abc24c6841f0a

Chunchun Zhang

Digitally signed by Chunchun Zhang
Date: 12/17/2021 10:34:59AM
GUID: 512696080000064178e75377202fe6c5d

FDA U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VI: BIOPHARMACEUTICS

IQA NDA Assessment Guide Reference

NDA Number	022388
Assessment Cycle Number	# 1
Drug Product Name/ Strength	ACUVUE® Theravision™ with Ketotifen (etafilcon A contact lens with ketotifen) (K-Lens)/ 0.019 mg per lens
Route of Administration	Ocular
Applicant Name	Johnson & Johnson Vision Care, Inc. (JJVCI)
Therapeutic Classification/OND Division	Division of Ophthalmology (DO)
LD Number	NDA 021066, ZADITOR (ketotifen fumarate ophthalmic solution, 0.025%)
Proposed Indication	To prevent itchy eyes due to allergies and correcting (b) (4) (b) (4) (myopia) or (b) (4) (hyperopia) in patients suitable for contact lens wear who do not have red eye(s) or more than 1.00D of astigmatism.
Primary Assessors	*Zhuojun Joan Zhao, Ph.D.*
Secondary Assessors	*Om Anand, Ph.D.*
Assessment	**Adequate**
Recommendation	Based on the assessment of the overall information, from a Biopharmaceutics perspective, NDA 022388 ACUVUE® Theravision™ with Ketotifen (etafilcon A contact lens with ketotifen) (K-Lens)/ 0.019 mg per lens, is recommended for **APPROVAL**.

Background

This 505(b)(2) application seeks approval for the proposed K-Lens, which is a drug device combination product, including the drug component (ketotifen fumarate solution (BKS)) and device component (Etafilcon A contact lens). Ketotifen fumarate, the drug component of this combination product, is the active ingredient in the currently marketed eye drop, ZADITOR® (NDA 021066).

The Biopharmaceutics review is focused on i) the evaluation and acceptability of the proposed quality control drug release method and acceptance criteria; and ii) the evaluation of the bridging between the manufacturing sites.

Drug release method and Acceptance Criteria:

Based on the provided drug release data, the following proposed drug release (ketotifen release kinetics) method, TM-0749, and acceptance criteria are found acceptable:

Ketotifen Release Kinetics Method TM-0749		Acceptance Criteria	
Medium	(b)% w/v boric acid, (b)% w/v sodium chloride, (b) (4) and (b) (4)% w/v pentetic acid	Sampling Time	% Ketotifen Released
Apparatus	USP Apparatus 4 with contact lens cell (b) (4)	5 minutes	(b) (4)%
Volume	60 mL	15 minutes	%
Rotation Speed	25 mL/min	30 minutes	%
Temperature	37ºC	90 minutes	NLT (b) (4)% (Q)

Bridging Manufacturing Sites

The K-Lens manufacturing process was initiated at JJVC in Jacksonville, Florida and the proposed commercial manufacturing facility is in Limerick, Ireland (JJVC-CP). As agreed during the IND stage, the Applicant provided sufficient data and justification to support the bridging the K-lens combination product manufactured in JJVC and JJVC-CP.

List Submissions being assessed:

Document(s) Assessed	Date Received
0001 (1) Original Submission	April 30, 2021
0015 (15) IR Response	November 1, 2021

Highlight Key Issues from Last Cycle and Their Resolution: NA

Concise Description of Outstanding Issues): None

B.1 DRUG SUBSTANCE

The drug substance, ketotifen fumarate, is a synthetic small molecule, same as the API in the LD product ZADITOR® (ketotifen fumarate) ophthalmic solution, 0.025% (NDA 021066).

Ketotifen fumarate has a reported solubility at pH 7.0 of 837 µg/mL. The concentration of ketotifen fumarate in the buffered ketotifen solution (BKS) is 43 µg/mL (Table 2), which is well below the solubility limit. Therefore, the polymorphism and particle size distribution of the drug substance is not considered to be a critical quality attribute.

B.2 DRUG PRODUCT

The proposed drug product, referred to as K-Lens, consists of an Etafilcon A soft hydrophilic contact lens (PMA N18-033) with 0.019 mg of ketotifen (Table 1).

Table 1: Composition of the proposed K-Lens

Component	Quality Reference	Function	Quantity
etafilcon A Contact Lens	Company Specification	Device Component	1 Device
Buffered Ketotifen Solution	Company Specification	Drug Component	(b) (4)
(b) (4)			

The drug component, ketotifen fumarate, is introduced via a buffered package solution (buffered ketotifen solution - BKS), as shown Table 2.

Table 2: Composition of Buffered Ketotifen Solution (BKS)

Component	Quality Reference	Function	(% w/w)
Ketotifen Fumarate	DMF (b) (4)	Active	0.0043
Pentetic Acid[a]	USP plus Company Specification	(b) (4)	
Calcium Hydroxide[a]	USP plus Company Specification		
Sodium Chloride	USP plus Company Specification		
(b) (4)	NF plus Company Specification		
Boric Acid	NF plus Company Specification		
Purified Water	USP plus Company Specification		
(b) (4)			

B.3 DRUG RELEASE METHOD

As recommended by the Agency in IND 66883, the Applicant developed Method TM-0749 to determine ketotifen release kinetics in K-Lens with multiple sampling time points. The proposed Ketotifen release kinetics in K-lens by HPLC-UV test method TM-0749 is using 60 mL release medium ((b) (4) at 25 mL/min in USP apparatus 4. The Applicant provided method development data for the choice of conditions in the Pharmaceutical Development Module 3.2.P.2.2.3.

(b) (4)

2 Pages have been Withheld in Full as b4 (CCI/ TS) immediately following this page

The Applicant concluded that the initial (b) (4) conditions were demonstrated suitable for the determination of K-Lens release kinetics and revised sampling volume and time points for method improvement, and the final release conditions are presented in Table 5.

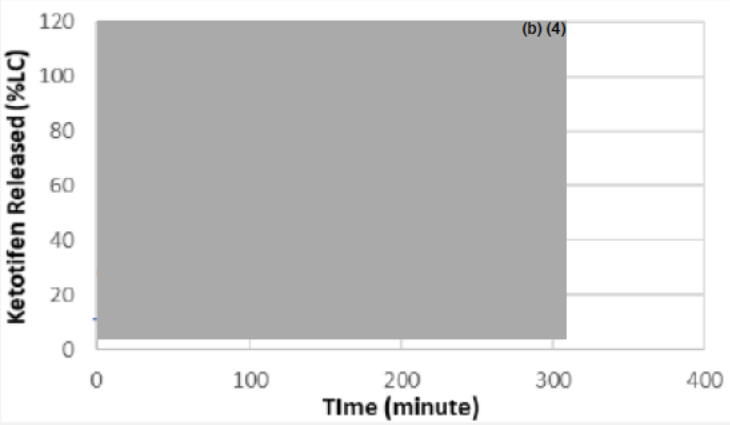
Table 5: K-Lens Release Kinetics Conditions

Parameter	Value
Apparatus	USP 4 ((b) (4)
Medium Volume	60 mL
Sample Cell Temperature	37°C
Bath Temperature	38.5°C
Media Flow Rate	25 mL/min
Sampling Volume[a]	1000 µL
Sampling Time Points[a]	5 min, 30 min, 60 min, 90 min and 120 min

Note: [a] Sampling volume and time points were modified during TM-0749 method development.

Figure 5 presents a ketotifen release profile obtained under the finalized (b) (4) condition along with an overlay of the profiles from initial and final release conditions.

Figure 5: Ketotifen Release Profile Under Updated (b) (4) Conditions (Orange) and Initial Conditions (Blue)



The ketotifen release profiles are similar between the initial and updated (b) (4) conditions. The Applicant accepted the updated conditions. Ketotifen released from K-Lens is more than 90% LC at 90 minutes; however, 120 minutes is included as an additional point for the profile.

Discriminating Power Assessment

The Applicant analyze K-Lens containing ketotifen < 17 µg and > 19 µg to determine the discriminating power of the proposed method TM-0749. The release profiles for the low and high concentration K-Lens were compared with the profile from nominal K-lens (19 µg/lens).

Discriminatory ability is demonstrated with f2 < 50 and f1 > 15 between the reference lot FR0F06 and testing lots FV8H06 (12.2 µg/lens) and FV8G06 (28.5% µg/lens). Table 6 and Table 7 present the release profile comparison results. For both the low and high lenses, the Applicant found f2 was < 50 and f1 was > 15.

Table 6: Discrimination Results Between Low and Nominal K-Lens

Time Point (min)	#FR0F06 (Nominal) Mean %Released (R_t)	#FV8H06 (Low Assay) Mean %Released (T_t)	Difference in Mean %Released (R_t-T_t)	(R_t-T_t)^2	Sum of (R_t-T_t)^2	Similarity Factor f2	Difference Factor f1
5	24.74	15.32	9.42	88.74			
15	50.56	31.30	19.26	370.95			
30	72.91	45.28	27.63	763.42	3639.00	28	37
90	92.33	61.85	30.48	929.03			
120	102.68	64.12	38.56	1486.8			

Note: (R_t-T_t) is expressed in absolute value terms.

Table 7: Discrimination Results Between High and Nominal K-Lens

Time Point (min)	#FR0F06 (Nominal) Mean %Released (R_t)	# FV8G06 (High Assay) Mean %Released (T_t)	Difference in Mean %Released (R_t-T_t)	(R_t-T_t)^2	Sum of (R_t-T_t)^2	Similarity Factor f2	Difference Factor f1
5	24.74	35.26	10.52	110.67			
15	50.56	72.36	21.80	475.24			
30	72.91	105.09	32.18	1035.55	6365.18	22	47
90	92.33	143.77	51.44	2646.07			
120	102.68	148.48	45.80	2097.64			

Note: (R_t-T_t) is expressed in absolute value terms.

Assessment: {Adequate}

The Applicant adequately demonstrated and justified the suitability of the proposed in vitro Ketotifen Release Kinetics Method TM-0749 for batch release and stability testing.

The Method TM-0749 shows some ability to detect variation in ketotifen content but no other critical CMC parameters were investigated. Therefore, the in vitro release kinetic method TM-0749 alone might not be sufficient to support formulation and process changes in the future.

B.4 DRUG RELEASE ACCEPTANCE CRITERIA

The Applicant proposed the following acceptance criteria as shown in Table 8.

Table 8: Proposed Ketotifen Drug Release Acceptance criteria

Sampling Time	% Ketotifen Released
5 minutes	(b) (4) %
15 minutes	%
30 minutes	%
90 minutes	NLT (b) (4) % (Q)

(b) (4)

. The corresponding lot numbers, manufacturing and test dates are listed in Table 9.

Table 9: K-Lens Lots Analyzed for Multi-Point Ketotifen Drug Release Characteristics

Sphere Power (Diopter)	K-Lens Lot	Date of Manufacture
-12.00D	X0004C1	October 2017
	X0005Z3	December 2018
	X0005LH	September 2018
	X0005LJ	September 2018
	X0007WP	September 2019
	X0007ZM	September 2019
	X00085P	September 2019
	X0005VZ	December 2018
-6.00D	X00048H	October 2017
	X0007WZ	September 2019
	X0007XV	September 2019
	X0007ZP	September 2019
+0.50D	X0005LG	September 2018
	X0005M1	September 2018
	X0005XT	December 2018
	X0005XX	December 2018

The Applicant summarized the results of statistical analysis of ketotifen drug release by lot and sampling time point for -12.00D, -6.00D and +0.50D lenses in Table 10.

Table 10: Summary Statistics of Drug Release Profile by Lot Number and Sampling Time Point

Sphere Power (Diopter)	K-Lens Lot	Time Point (Minutes)	N[a]	Mean (%)	Std Dev (%)	Minimum (%)	Maximum (%)
-12.00D	X0004C1	5	18	28.78	2.26		(b) (4)
		15	18	52.41	2.12		
		30	18	73.75	1.88		
		90	18	97.66	1.64		
		120	18	100.24	1.58		
	X0005LH	5	6	22.18	0.77		
		15	6	46.08	1.66		
		30	6	66.84	1.94		
		90	6	93.25	1.50		
		120	6	96.79	1.33		
	X0005LJ	5	6	22.90	0.97		
		15	6	47.25	1.13		
		30	6	68.53	1.49		
		90	6	94.20	1.84		
		120	6	97.62	1.78		
	X0005VZ	5	18	24.56	1.68		
		15	18	49.56	1.74		
		30	18	71.87	1.71		
		90	18	98.35	1.25		
		120	18	102.37	1.42		
	X0005Z3	5	18	22.10	0.97		
		15	18	45.92	1.94		
		30	18	66.68	2.14		
		90	18	92.25	1.38		
		120	18	95.57	1.41		
	X0007WP	5	6	22.07	0.47		
		15	6	46.12	0.77		
		30	6	66.71	1.61		
		90	6	93.38	1.81		
		120	6	97.72	1.56		
	X0007ZM	5	6	22.42	0.86		
		15	6	47.98	0.98		
		30	6	70.41	1.21		
		90	6	96.73	1.49		
		120	6	99.77	1.48		
	X00085P	5	6	22.81	0.76		
		15	6	46.99	1.32		
		30	6	67.69	1.89		
		90	6	94.04	1.01		
		120	6	97.51	0.94		

(Continued)

Sphere Power (Diopter)	K-Lens Lot	Time Point (Minutes)	N[a]	Mean (%)	Std Dev (%)	Minimum (%)	Maximum (%)
			(Continued)				(b) (4)
-6.00D	X00048H	5	6	25.31	1.56		
		15	6	51.70	2.26		
		30	6	73.32	2.86		
		90	6	93.74	3.82		
		120	6	95.78	3.64		
	X0007WZ	5	6	23.41	0.83		
		15	6	48.64	1.49		
		30	6	70.34	1.52		
		90	6	94.73	1.61		
		120	6	97.31	1.48		
	X0007XV	5	6	24.97	1.04		
		15	6	51.30	1.49		
		30	6	72.72	1.88		
		90	6	94.15	1.03		
		120	6	96.14	1.11		
	X0007ZP	5	6	23.17	1.17		
		15	6	48.74	1.46		
		30	6	71.09	1.86		
		90	6	95.17	1.33		
		120	6	97.74	1.40		
+0.50D	X0005LG	5	6	28.05	1.18		
		15	6	56.30	0.78		
		30	6	77.83	1.07		
		90	6	96.30	0.91		
		120	6	97.71	0.60		
	X0005M1	5	6	27.30	0.66		
		15	6	55.41	1.19		
		30	6	76.98	1.75		
		90	6	95.25	1.14		
		120	6	96.52	0.97		
	X0005XT	5	18	27.01	1.94		
		15	18	54.32	2.89		
		30	18	75.92	3.05		
		90	18	94.36	3.05		
		120	18	96.37	3.40		
	X0005XX	5	18	28.63	1.88		
		15	18	57.62	1.99		
		30	18	79.89	1.77		
		90	18	97.36	1.42		
		120	18	99.10	1.16		

[a] Number of Samples

A plateau was reached at 90 minutes (Figure 6 and Figure 7). As a result, The Applicant selected the sampling time points at 5, 15, 30, and 90 minutes to encompass the early, intermediate, and final time points of the drug release profile.

Figure 6: Drug Release Profile of -12.00D, -6.00D and +0.50D Lenses

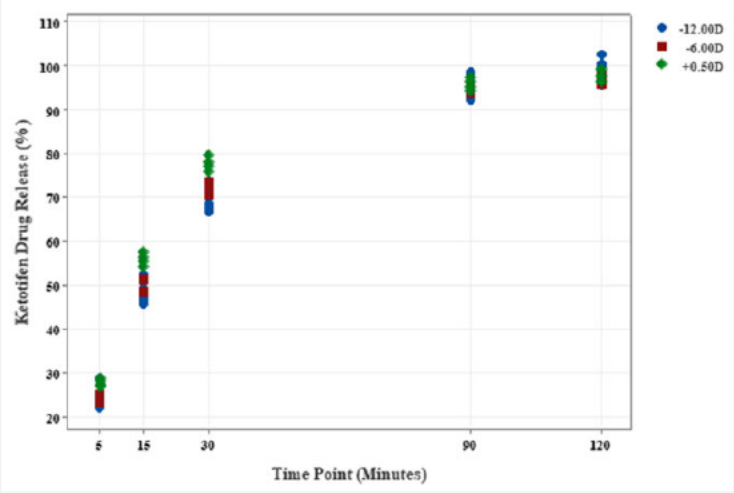
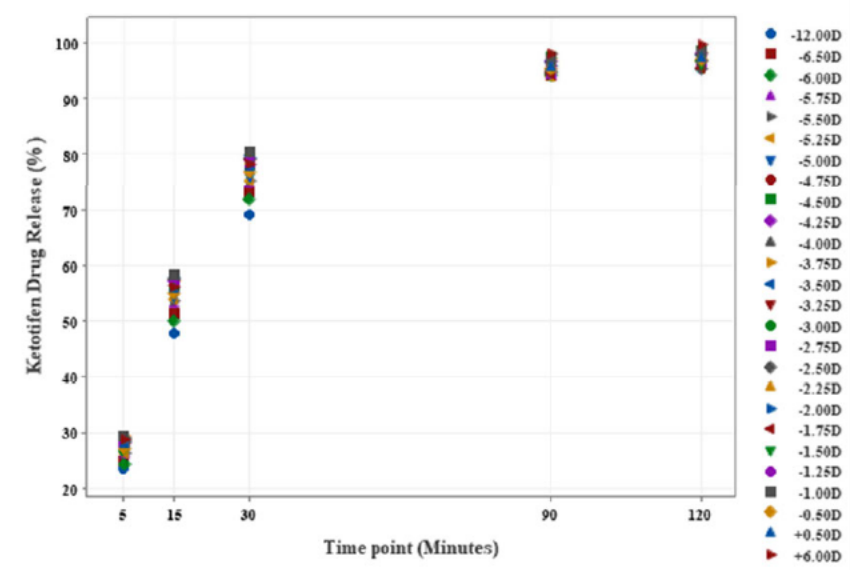


Figure 7: Ketotifen Drug Release Profile for K-Lens Sphere Powers



Assessment: {Adequate}

Based on the provided Ketotifen release profiles, the proposed acceptance criteria in Table 8 are acceptable.

B.4 BRIDGE BETWEEN THE PROPOSED DRUG PRODUCT AND THE LISTED DRUG PRODUCT

The Applicant investigated fifteen BKS formulations in non-clinical and clinical studies during the development of K-Lens (**Table 11**).

Table 11: Composition of the BKS Formulations Used in K-Lens Non-Clinical and Clinical Studies

Formula Number	BKS Formulation[a]									K-Lens Dose
	Sodium Chloride	Boric Acid	(b) (4)	(b) (4)	(b) (4)	Calcium Hydroxide	Pentetic Acid	(b) (4)	Purified Water	Ketotifen Fumarate	Ketotifen Assay (mg/lens)
											(b) (4)

The final formulation (Table 2), shown as Formulation Number 15 in Table 11, was evaluated in Phase 3 "Additional Pivotal Safety" (CR-4539) clinical study, while Formulation Number 8 was evaluated in Phase 3 "Pivotal Efficacy CAC" studies (CR-4483 and CR-4484).

In addition, the development of the K-Lens manufacturing process was initiated at JJVC in Jacksonville, Florida and transferred to the combination product manufacturing facility in Limerick, Ireland (JJVC-CP) where the product will be commercialized. (b) (4)

The K-Lens build protocols described in Table 12 represent a range of lens powers built based on the study requirements. These lens powers could range from –12.00D to +6.00D within a given protocol. K-Lens contains the same amount of ketotifen across the full range of lens powers (0.019 mg/lens), therefore, the Applicant chosen a common lens power range of –1.00D to +1.00D to represent K-Lens for comparison across the studies.

Table 12: K-Lens Produced for Phase 3 Clinical Studies, Registration Stability and Process Validation

K-Lens Build Protocol	Manufacturing Site		Usage
	JJVC	JJVC-CP	
07CP1000	✓		Phase 3 Clinical Studies (Safety & Efficacy)
07CP1020	✓		Phase 3 Clinical Studies (Safety)
07CP1066	✓		Phase 3 Clinical Studies (Safety)
09CP1022	✓		Phase 3 Clinical Studies (Safety)
09CP1099	✓		Phase 3 Clinical Studies (Safety)
17CP1049		✓	Device Design Validation Study
19CP1082		✓	Registration Stability Study
19CP1028		✓	Process Validation
19CP1176		✓	Process Validation
20CP2099		✓	Process Validation
20CP2217		✓	Process Validation

The Applicant tested the ketotifen identification, ketotifen assay, ketotifen content uniformity, ketotifen degradation products, sterility, pH, and osmolality using the analytical method and specification in place at the time of testing (Table 13).

Table 13: K-Lens Drug Properties Results Summary

Test Parameter	Phase 3 Clinical Studies	Device Design Validation	Registration Stability Study	Process Validation
Ketotifen Identification (Lens) HPLC Retention Time	Pass	Pass	Pass	Pass
Ketotifen Identification (Lens) UV Spectrum Match	NA[a]	Pass	Pass	Pass
Ketotifen Assay	Pass	Pass	Pass	Pass
Content Uniformity	Pass	Pass	Pass	Pass
Ketotifen Drug Release Single Point	Pass	NA	NA	NA
Ketotifen Drug Release Multipoint	NA	Pass	Pass	Pass
Ketotifen Degradation Products: Individual Specified	Pass	Pass	Pass	Pass
Ketotifen Degradation Products: Individual Unspecified	Pass	Pass	Pass	Pass
Ketotifen Degradation Products: Total	Pass	Pass	Pass	Pass
Sterile (Package Integrity)	Pass	Pass	Pass	Pass
Finished package solution pH	Pass	Pass	Pass	Pass
Finished package solution Osmolality	Pass	Pass	Pass	Pass

[a] The test was not a product release requirement at the time tested

NA = Not applicable

It is noted that the ketotifen drug release test for the K-Lens lots in protocols 07CP1000, 07CP1020, and 07CP1066 were tested using a single point HPLC-UV method. The K-Lens lots in protocol 17CP1049, 19CP1082, 19CP1028, 19CP1176, 20CP2099 and 20CP2217 were tested using a multipoint drug release method using a USP Apparatus 4 and HPLC-UV method. At the time the process validation was conducted, the multipoint drug release acceptance criteria were not finalized. While all of the time points were tested, only the 90-minute timepoint was reported with an acceptance criterion of ≥ (b) (4)% ketotifen release.

The Applicant concluded that K-Lens build protocols made at JJVC-CP (registration stability, device design validation, and process validation) met the specifications in place at the time of the builds and are comparable to the build protocols executed at JJVC for the Phase 3 clinical studies.

Reviewer's Assessment:

The (b) (4) in Formulation Number 8 is considered the same as (b) (4) in the final formulation (Formulation Number 15) by Drug Product Reviewer Dr. Milton Sloan. Therefore, there is no need to do bridging for the formulations.

The Applicant also provided adequate data and justification supporting the bridging of the K-lens combination product manufactured in JJVC and JJVC-CP in the original submission and the amendment dated November 1, 2021 (Appendix 1).

3 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

Zhuojun Zhao

Digitally signed by Zhuojun Zhao
Date: 12/20/2021 10:26:53PM
GUID: 508da6fd000284770cf4eecbae074722

Om Anand

Digitally signed by Om Anand
Date: 12/21/2021 09:10:24AM
GUID: 508da6fb0002833385a1485d53137893

CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	022388
Assessment Cycle Number	MR01
Drug Product Name/ Strength	Etafilcon A Lens with Ketotifen (0.019 mg/lens) (b) (4)
Route of Administration	Ocular
Applicant Name	Johnson & Johnson Vision Care, Inc.
Therapeutic Classification/ OND Division	Division of Ophthalmics
Manufacturing Site	Johnson & Johnson Vision Care, Inc. The National Technology Park Limerick, Ireland V94 H97W
Method of Sterilization	(b) (4)

Assessment Recommendation: **Adequate**

Assessment Summary:

List Submissions being assessed (table):

Document(s) Assessed	Date Received
ECTD Sequence 0001 (ORIG-1)	4/30/2021
ECTD Sequence 0007 (ORIG-1/Quality/Response to Information Request)	6/25/2021
ECTD Sequence 0013 (ORIG-1/Quality/Response to Information Request)	10/13/2021
ECTD Sequence 0016 (ORIG-1/Quality/Response to Information Request)	11/8/2021
ECTD Sequence 0017	12/1/2021

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: The drug product (K-Lens) is a drug/device combination. Buffered Ketotifen (BKS – (b) (4) is added to the manufacture of the device component which consists of a contact lens. This is then packaged into a blister pack and (b) (4) sterilized. The applicant is proposing to (b) (4)

The applicant noted that ketotifen, the drug component of the combination product, is the active ingredient in the currently marketed eye drop, ZADITOR® manufactured by Alcon Pharmaceuticals and originally approved under NDA 210166. It is currently OTC. The device component is a disposable contact lens currently marketed as 1-DAY ACUVUE® Brand Contact Lens (etafilcon A) and based on device submission PMA N18-033.

Concise Description of Outstanding Issues: N/A

Supporting Documents: None.

S DRUG SUBSTANCE

The drug substance is not provided sterile. Therefore, a product quality microbiology review of the drug substance is not performed.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

(Sequence 0001, Module 3.2.P.1 Description and Composition of the Drug Product)
(Sequence 0001, Module 3.2.P.7, Container Closure System – K-Lens)

- **Description of drug product –** The drug/device combination product consists of a [redacted] (b) (4) soft hydrophilic contact lens with buffered ketotifen (clear & colorless) solution (0.019 mg of ketotifen). It is supplied as a single-unit dose in a blister bowl with lidstock [redacted] (b) (4) [redacted]. The container closure system remains the same for the 3 different [redacted] (b) (4) units.

  The applicant provided the following information for the components of the product:
  - **Device component:** The device is an etafilcon A soft contact lens (PMA N18-033 is referenced for manufacturing information) with an optical design based on the 1-Day Acuvue Brand Contact Lens.[redacted] (b) (4) [redacted]), which is used to manufacture the device component of K-Lens.
  - **Drug component:** Ketotifen fumarate is introduced via a buffered package solution (buffered ketotifen solution, or BKS).
  - **K-Lens:** Formed by combining the device component with the BKS [redacted] (b) (4) [redacted] to form the final drug product.

- **Drug product composition –**
  Composition of [redacted] (b) (4)

Component	Function	Quantity (% w/w)

2-hydoxyethyl Methacrylate (HEMA) Methacrylic acid (MAA) Ethylene Glycol Dimethacrylate (EGDMA) 1,1,1-Trimethylolpropane Trimehtyacrylate (TMPTMA)		(b) (4)
(b) (4)		
Blue 2-Hydroxyethyl Methacrylate (Blue HEMA)	Visibility Tint	(b) (4)

(b) (4)

Composition of Buffered Ketotifen Solution (BKS)

Component	Function	Quantity (% w/w)
Ketotifen Fumarate	Active	0.0043
Pentetic Acid	(b) (4)	
Calcium Hydroxide		
Sodium Chloride		
(b) (4)		
Boric Acid		
Purified Water		

Composition of K-Lens

Component	Function	Quantity
etafilcon A Contact Lens	Device Component	1 device
Buffered Ketotifen Solution	Drug Component	(b) (4)

- **Description of container closure system –**

Configuration	Component	Description	Manufacturer
K-Lens in single blister pack	Blister	(b) (4)	(b) (4)
	Lidstock	(b) (4) laminated foil (b) (4)	(b) (4)

Note: the blister bowl and lidstock (b) (4)

30 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

2. ASSESSMENT OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Prescribing Information

(Sequence 0001, Module 1.14.1.3 Draft Clean Package Insert and Professional Fitting and Information Guide)
(Sequence 0001, Module 3.2.P.8.1 Stability Summary and Conclusion)

Storage temperature: 15 – 25°C; with excursions permitted up to 30°C
Maximum storage time: 18 months
Route of administration: Ocular

Container: Single-unit dose

Assessment: *Adequate*

The applicant has met regulatory expectations regarding the information related to issues of product quality microbiology that is provided in the product labeling.

MICROBIOLOGY LIST OF DEFICIENCIES

Not applicable.

Primary Microbiology Assessor Name and Date:
Valerie A. Huse, PhD; 3 September 2021
Laura R. Wasil, PhD; 9 December 2021

Secondary Assessor Name and Date (and Secondary Summary, as needed):
Christine Craig, PhD; 9 December 2021

Christine Craig

Digitally signed by Christine Craig
Date: 12/09/2021 10:35:18AM
GUID: 57ced2690109ab449e84a49141df01f8

Laura Wasil

Digitally signed by Laura Wasil
Date: 12/09/2021 09:38:51AM
GUID: 59b190cf009be8467b9b6b02d9543afe

59 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

CHUNCHUN N ZHANG
12/21/2021 07:45:51 PM