Cross-Discipline Team Leader and Division Director Review of NDA 22388

Review Completion Date	See DARRTS Stamp Date
From	William M. Boyd, M.D., Wiley Chambers, M.D.
Subject	Cross-Discipline Team Leader and Division Director Review
NDA #	22-388
Applicant	Johnson and Johnson Vision Care, Inc.
Date of Submission	April 30, 2021
PDUFA Goal Date	February 28, 2022
Proprietary Name	ACUVUE Theravision with Ketotifen
Established or Proper Name	etafilcon A drug-eluting contact lens with ketotifen
Dosage Form(s)	drug-eluting contact lens
Recommended Indication/Population	Indicated for the prevention ocular itch due to allergic conjunctivitis and correction of refractive ametropia (myopia and hyperopia) in patients who do not have red eye(s), are suitable for contact lens wear and do not have more than 1.00 D of astigmatism
Dosing Regimen(s)	• One ACUVUE Theravision with Ketotifen should be inserted per eye per day. • Discard lens after a single day's use. • ACUVUE Theravision with Ketotifen may be worn beyond twelve hours for vision correction. • Lenses should be removed prior to sleeping.
Regulatory Action	Approval

Reviewers/Consultants	**Names of Discipline Reviewers**
OND RPM	Ahmed Ayodeji
CDTL	William Boyd
Division Director	Wiley Chambers
Clinical Reviewer	Rhea Lloyd
Pharmacology Toxicology Reviewer	Erin Ruhland
Statistical Reviewer	Abel Eshete
Clinical Pharmacology Reviewer	Amit Somani
OND Labeling Reviewer	Derek Alberding
CDRH Reviewer	Kimberly Lewandowski-Walker
OPQ Drug Substance Reviewer	Ben Zhang
OPQ Drug Product Reviewer	Milton Sloan
OPQ Microbiology Reviewer	Laura Wasil
OPQ Biopharmaceutics	Joan Zhao
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CDTL=Cross-Discipline Team Leader
DMEPA=Division of Medication Error Prevention and Analysis
OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion

1. Summary

ACUVUE Theravision with Ketotifen (etafilcon A drug-eluting contact lens with ketotifen), also referred to as K-Lens within this review, is a combination product that contains ketotifen fumarate, an antihistamine, and a daily disposable etafilcon A contact lens. Several different K-Lens formulations were tested during the clinical development program. The nominal dose of 0.019 mg ketotifen/lens (represented as K-Lens 25) was included in all 13 clinical studies, which is the proposed commercial dose.

Ketotifen fumarate is the active ingredient in several currently marketed over-the-counter (OTC) ophthalmic medications indicated for the prevention of ocular itching associated with allergic conjunctivitis. It is a relatively selective H_1 antihistamine/mast cell stabilizer.

This is a 505(b)(2) new drug application with reliance on NDA 21-066 (Zaditor; Alcon Research Ltd) for aspects of nonclinical systemic safety of ketotifen fumarate.

The etafilcon A (FDA Group IV), soft hydrophilic contact lens is a daily disposable contact lens. Etafilcon A is a copolymer of 2-hydroxyethyl methacrylate and methacrylic acid cross linked with 1,1,1-trimethylol propane trimethacrylate and ethylene glycol dimethacrylate. The lenses are tinted with (b) (4) to improve visibility and handling.

NDA 22388 will be approved with the labeling found in this review. The application supports the safety and effectiveness of ACUVUE Theravision with Ketotifen (etafilcon A contact lens with ketotifen) for the prevention ocular itch due to allergic conjunctivitis and correction of refractive ametropia (myopia and hyperopia) in aphakic and/or phakic patients who do not have red eye(s), are suitable for contact lens wear and do not have more than 1 D of astigmatism.

Reference ID: 4943321

2. Benefit-Risk Assessment

Benefit-Risk Dimensions

Benefit-Risk Integrated Assessment

The adequate and well controlled studies contained in this submission establish the efficacy of ACUVUE Theravision with Ketotifen (etafilcon A drug-eluting contact lens with ketotifen), nominal dose of 0.019 mg ketotifen/lens, for prevention ocular itch due to allergic conjunctivitis and correction of refractive ametropia (myopia and hyperopia) in patients who do not have red eye(s), are suitable for contact lens wear and do not have more than 1.00 D of astigmatism.

Studies CR-4483 and CR-4484 demonstrated superiority of ACUVUE Theravision with Ketotifen compared to ACUVUE daily contact lens (without ketotifen) for the intended indication. The most common ocular adverse events after treatment with ACUVUE Theravision with Ketotifen observed in the submitted clinical studies were eye irritation, eye pain, instillation site irritation, dry eye, photophobia and mydriasis.

There is a favorable benefit-risk ratio of ACUVUE Theravision with Ketotifen (etafilcon A contact lens with ketotifen) for the prevention of ocular itch due to allergic conjunctivitis who do not have red eye(s) and correction of refractive ametropia (myopia and hyperopia) in patients who are suitable for contact lens wear or more than 1.00 D of astigmatism.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Ocular allergies affect more than 20% of the general population.	The goal of treatment of ACUVUE Theravision with Ketotifen is to prevent ocular itching in patients who have refractive ametropia and are contact lens wearers.
Current Treatment Options	• There are no combination antihistamine and contact lens therapies approved. • Many topical ophthalmic antihistamines are approved for the treatment of ocular allergies. These therapies require contact lens wearers to wait at least 10 minutes after instillation before lens insertion to prevent absorption of benzalkonium chloride by soft contact lenses.	ACUVUE Theravision with Ketotifen was superior to ACUVUE daily contact lens alone in the prevention of ocular itch due to allergic conjunctivitis. This product, if approved, would provide a new therapeutic option for contact lens wearers.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Studies CR-4483 and CR-4484 demonstrated that ACUVUE Theravision with Ketotifen was superior to ACUVUE daily wear contact lens without ketotifen (placebo lens) in the prevention of ocular itch due to allergic conjunctivitis in conjunctival allergen challenge studies with an onset of action as soon as 3 minutes post-CAC and a duration of action of up to 12 hours of lens wear. • When used as clinically indicated, K-Lens is safe for use in patients with refractive ametropia (myopia and hyperopia) and allergic conjunctivitis. No clinically significant or unexpected ocular or non-ocular AEs were identified in clinical studies. The use of K-Lens did not appear to negatively affect visual acuity.	Adequate and well controlled studies support the efficacy the prevention of ocular itch due to allergic conjunctivitis in contact lens wearers.
Risk and Risk Management	• Ocular allergies can cause ocular hyperemia. K-Lens is intended to be used prior to the onset of the ocular allergic symptoms. As such, (b) (4) specifies that K-Lens is to be used in patients without ocular hyperemia. • The proposed product labeling contains a contraindication and a warning against wearing lenses if eye(s) are red and instructs patients to remove lenses immediately if eye(s) become red while wearing the lenses. • ACUVUE Theravision with Ketotifen in studies CR-4483, CR-4484, CR-4490, and CR-4590 demonstrated an acceptable safety profile.	Routine monitoring and reporting of all adverse events are expected to be adequate to monitor for potential new adverse reactions.

3. Background

Ocular allergies affect > 20% of the general population. These disorders are immunoglobulin E (IgE)-dependent (Type 1) hypersensitivity inflammatory responses and primarily include seasonal allergic conjunctivitis and perennial allergic conjunctivitis. In susceptible individuals, ocular exposure to an allergen triggers an inflammatory cascade that is spurred primarily by histamine release and culminates in the characteristic signs and symptoms of ocular allergy disorders: itching, redness, swelling of the eyelid, chemosis, and tearing.

There is no currently approved combination treatment for both refractive ametropia and ocular itching associated with allergic conjunctivitis. ACUVUE Theravision with Ketotifen (etafilcon A contact lens with ketotifen) was launched in Canada, on May 10, 2021, and in Japan, on June 25, 2021.

Table 3.1: Summary of K-Lens US FDA Interactions

Interaction Type	Primary Purpose of Interaction	Date
Pre-IND Meeting	Clinical, CMC	24 November 2003
RFD Acceptance	Request for Designation	15 July 2004
End of Phase 2 Meeting	Clinical, CMC	1 December 2006
Type B Meeting	Clinical	25 June 2008
Type B Meeting	CMC	3 October 2008
Type C Meeting	Clinical, Parametric Release	20 October 2009 (WRO)
Type C Meeting	Clinical	26 April 2011
Type C Meeting	CMC, Non-Clinical	9 May 2014
Type C Meeting	CMC	5 November 2015
Type C Meeting	Clinical, CMC	13 June 2017
Type C Meeting	Labeling, Advisory Committee	8 17 February 2021
Type B Meeting	Pre-NDA	23 March 2021 (WRO)

Abbreviations: CMC=chemistry, manufacturing, and controls; IND=investigational new drug; NDA=new drug application; RFD=request for designation; WRO=written responses only

4. Product Quality

OPQ completed their original integrated review of the original application on 12/21/2021.

The combination product, referred to as K-Lens, consists of an etafilcon A soft hydrophilic contact lens with 0.019 mg of ketotifen. This is considered a single entity combination product. Additional information pertaining to the drug and device components is listed below:

- Device component – The device component is an etafilcon A soft contact lens, which uses the materials and manufacturing methods described in PMA N18-033, with an optical design based on the of 1•DAY ACUVUE® Brand Contact Lens. (b) (4) used to manufacture the device component of K-Lens.

- Drug component – The drug component, ketotifen fumarate, is introduced via a buffered package solution (buffered ketotifen solution - BKS).

- K-Lens – K-Lens is formed by combining the device component with the BKS (b) (4) to form the final drug product.

4.1. Combination Product Composition

Composition (b) (4)

Component	Function	(% w/w)
2-Hydroxyethyl Methacrylate (HEMA)	(b) (4)	
Methacrylic acid (MAA)		
Ethylene Glycol Dimethacrylate (EGDMA)		
1,1,1-Trimethylolpropane Trimethacrylate (TMPTMA)		
(b) (4)		
Blue 2-Hydroxyethyl Methacrylate (Blue HEMA)	Visibility Tint	(b) (4)
(b) (4)		

(b) (4)

Composition of Buffered Ketotifen Solution (BKS)

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

Composition of K-Lens

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

Source: Module 2.3.P.1 Description and Composition of the Drug Product

4.2. Product Specifications

Table 1: Specifications for K-Lens

Test Parameter	Acceptance Criteria	Test Methods
	Chemical Attributes	
1. Ketotifen Identification (Lens): HPLC	Retention Time of Main Peak in Sample Matches Main Peak in Ketotifen Reference Standard	TM-0572
2. Ketotifen Identification (Lens): UV	UV Spectrum of Main Peak in Sample Matches Spectrum of Main Peak in Ketotifen Reference Standard	TM-0572
3. Ketotifen Assay	(b) (4) mg/lens)	TM-0572
4. Content Uniformity	Conforms to USP <905>	TM-0572
5. Ketotifen Degradation Products		TM-0572
a. Individual specified degradation products	(b) (4) wt%	
i. Ph. Eur. D (N-oxide)		
ii. (b) (4)		
iii. Ph. Eur. G		
b. Individual unspecified degradation products	(b) (4) wt%	
c. Total degradation products	(b) (4) wt%	
6. Ketotifen Drug Release	No individual value lies outside each of the stated ranges, and no individual value is less than the stated amount at the final test time. (b) (4)	TM-0749
7. Finished Package Solution pH	6.6–7.3	USP <791>
8. Finished Package Solution Osmolality	(b) (4) 460 mOsm/Kg	USP <785>

(Continued)

Table 1: Specifications for K-Lens

Test Parameter	Acceptance Criteria	Test Methods
	(Continued)	
	Device Attributes	
1. Lens Appearance	Contact lens with blue visibility tint with clear, colorless solution	Visual
2. Diameter	(b) (4) mm	TM-0700
3. Sphere (Vertex) Power	(b) (4)	TM-0700
4. Base Curve Radius		TM-0701
5. Center Thickness		TM-0701
6. Water Content		TM-0589
7. Wet Refractive Index of Hydrated Lens		TM-0589
8. Average Visible Light Transmittance (luminous 380-780 nm)		TM-0443
9. Average Ultraviolet Light Transmittance UVA 316-380 nm		TM-0443
10. Average Ultraviolet Light Transmittance UVB 280-315 nm		TM-0443
11. Sterility		Parametric Release
12. Cosmetic Visual Attribute 1[a]	The package must contain one and only one contact lens.	QP-0075

(Continued)

Table 1: Specifications for K-Lens

Test Parameter	Acceptance Criteria	Test Methods
	(Continued)	
13. Cosmetic Visual Attribute 2[a]	(b) (4)	QP-0075
14. Cosmetic Visual Attribute 3[a]		QP-0075

[a] Performed at release only

Source: Module 3.2.P.5.1 Specification(s)

Test methods, validations, and justifications of specifications for the device attributes are approved in PMA N18-033 and thus were not provided in this NDA.

4.3. Microbiology

The applicant has provided adequate sterility assurance. No approvability issues were identified from a sterility assurance or microbiology product quality perspective.

4.4. CDRH

ACUVUE Theravision with Ketotifen (etafilcon A drug-eluting contact lens with ketotifen) is a drug/device combination product with CDER as the lead Center. CDRH, Contact Lenses and Dry Eye Devices Team, Office of Product Evaluation and Quality, completed a consultative review on August 16, 2021. The Package Insert/Professional Fitting Guide, Patient Instructions, and carton and blister labeling were noted and reviewed by CDRH.

The device is a daily wear, daily disposable soft hydrophilic contact lens consisting of etafilcon A with ketotifen. The device component of K-Lens is the etafilcon A (FDA Group IV), soft hydrophilic daily disposable contact lens. Etafilcon A is a copolymer of 2-hydroxyethyl methacrylate and methacrylic acid cross linked with 1,1,1-trimethylol propane trimethacrylate and ethylene glycol dimethacrylate. The lens parameters were found to be consistent with previously cleared daily disposable lenses marketed by this firm (K051900; K062614).

4.5. Establishment Information

The Pre-Approval Inspections of Ortec, Inc (FEI: 3004285326) and Johnson & Johnson Ireland (FEI: 3003083595) were conducted and found acceptable. The Office of Pharmaceutical Manufacturing Assessment (OPMA) issued an overall acceptable recommendation for all the facilities on 2/24/2022.

Facility name and address	FEI	Responsibilities and profile code(s)	Status
Olon S.p.A. Via Livelli, 1 26852 Casaletto Lodigiano, Mairano , LO, Italy, N/A	3002808159	Synthesis of Drug Substance || DMF: (b) (4) || 356h Status: Pending CSN	Approve - Based on Previous History
Johnson & Johnson Vision Care, Inc. 7500 Centurion Parkway , Jacksonville, FL, USA, 32256	1000222023	Manufacturing (b) (4) || 356h Status: Pending OPT – Optic fabrication and assembly Note: (b) (4)	Approve - Based on Previous History (CDRH memo)
Ortec Inc. 465 Old Pelzer Rd. , Piedmont, SC, USA, 29673	3004285326	Manufacturing (b) (4) || 356h Status: Pending (b) (4)	Approve - Based on PAI
Johnson & Johnson Vision Care Ireland UC The National Technology Park , Limerick, Limerick, Ireland, V94 N732	3003083595	Manufacturing of etafilcon A lens with ketotifen || 356h Status: Pending OPT – Optic fabrication and assembly SLQ	Approve - Based on PAI
(b) (4)		Stability Storage || 356h Status: Pending (b) (4) Note: Module 3 indicates (b) (4) provides stability storage (b) (4)	Approve - Based on 704(a)(4)

4.6. Recommendation on Phase 4 (Post-Marketing) Commitments, Requirements, Agreements, and/or Risk Management Steps

There are no post-marketing commitments or requirements recommended.

4.7. OPQ Recommendation

NDA 022388 is recommended for approval from Product Quality perspective.

5. Nonclinical Pharmacology/Toxicology

From the original Nonclinical Pharmacology/Toxicology Review dated 12/27/2021:

The Applicant conducted nonclinical ocular toxicity studies to support the ocular safety of the proposed drug/device combination. The Applicant has filed a 505(b)(2) NDA with reliance on NDA 021066 (Zaditor; Alcon Research Ltd) for aspects of nonclinical systemic safety of ketotifen fumarate. An adequate bridge for systemic safety is established by a large dose margin between API doses used in those studies relied upon and the content of the API in the drug/device combination.

The Acuvue K-lens containing up to 0.038 mg ketotifen per lens (2x proposed formulation content) was not associated with ocular toxicity in rabbits administered the lens once daily for 6 months. Slight ocular irritation of the lens (and placebo lens) was indicated by conjunctival redness and slight lymphocytic infiltrates. The novel excipient, (b) (4), was qualified as non-genotoxic in *in vitro* assays and showed no signs of toxicity in rabbits following ocular instillation of the lens.

There are no adequate and well-controlled studies of ACUVUE Theravison with Ketotifen administration in pregnant women to inform a drug-associated risk. ACUVUE Theravison with Ketotifen is not absorbed systemically following ocular administration, and maternal use is not expected to result in fetal exposure to the drug. Oral administration of ketotifen fumarate to pregnant rats or rabbits did not produce teratogenicity at clinically relevant doses.

No information is available on the carcinogenic potential of ketotifen fumarate.

6. Clinical Pharmacology

No human pharmacokinetic study with the proposed to-be-marketed product was performed during the clinical development program. As noted in the minutes for the IND 66883 meeting held on May 9, 2014, ocular pharmacokinetic (PK) work for this product in humans is impracticable due to exposure generally below the quantitation limit of assay.

7. Clinical Efficacy

From the original Medical Officer Review dated 2/23/2022:

Clinical data for Studies CR-4483 and CR-4484 were reviewed to support efficacy.

Study CR-4483 Efficacy Results – Primary Endpoint

Table 6.1.2-6 Summary (Continuous Analysis) of Ocular Itching at Visits 4 and 5 (ITT Population)

Visit Time point	Treatment [a]		Difference[b]	P value[c]
	Placebo (N=121)	K-Lens (N=119)		
Visit 4 (12 hour)	121	119		
Pre-Challenge Mean (SD)	0	0	0	
Post-Challenge	119	117		
3 Min Mean (SD)	1.71 (0.89)	0.61 (0.70)	-1.10	<0.001
5 Min Mean (SD)	1.96 (0.90)	0.74 (0.73)	-1.22	<0.001
7 Min Mean (SD)	1.86 (0.94)	0.79 (0.79)	-1.07	<0.001
Visit 5 (15 minute)	112	113		
Pre-Challenge Mean (SD)	0	0.01 (0.07)	0.01	0.158
3 Min Mean (SD)	1.60 (0.87)	0.42 (0.66)	-1.18	<0.001
5 Min Mean (SD)	1.82 (0.92)	0.56 (0.71)	-1.26	<0.001
7 Min Mean (SD)	1.69 (0.95)	0.54 (0.70)	-1.15	<0.001

Source data: Module 5.3.5.1, Study CR-4483 CSR Section 14.1, Table 6.1b

[a]Individual eye was the unit of analyses.

[b]Difference was K-Lens minus placebo; a negative difference favors K-Lens. If data were missing within a visit, the LOCF method was used.

[c]*P* value was based on two-sample t-test comparing K-Lens to placebo. NC = not calculated.

Note: At Visit 4, approximately 12 hours post-lens insertion and at Visit 5, 15 minutes post-lens insertion, the subject underwent CAC, then the subject evaluated itching on the following 0 to 4 scale:
0 = None;
0.5 = An intermittent tickle sensation possibly localized in the corner of the eye;
1.0 = An intermittent tickle sensation involving more than just the corner of the eye;
1.5 = Intermittent all-over tickling sensation;
2.0 = A mild continuous itch (could be localized) without desire to rub;
2.5 = Moderate, diffuse continuous itch with desire to rub;
3.0 = A severe itch with desire to rub;
3.5 = Severe itch improved with minimal rubbing; or
4.0 = Incapacitating itch with an irresistible urge to rub.

A clinically and statistically significant reduction in ocular itching scores was achieved by the K-Lens treated eyes compared with placebo-treated eyes at both Visit 5, the onset of action (Visit 5, challenge at 15 minutes after lens insertion) and Visit 4, the duration of action (challenge at 12 hours after lens insertion) study visits.

Study CR-4484 Efficacy Results – Primary Endpoint

Table 6.2.2-7 Summary (Continuous Analysis) of Ocular Itching at Visits 4 and 5 (ITT Population)

Visit Time point	Treatment[a] Placebo (N=125)	 K-Lens (N=123)	 Difference[b]	 *P* value[c]
Visit 4 (12 hour)				
Pre-Challenge				
n	125	123		
Pre-Challenge Mean (SD)	0.00 (0.00)	0.00 (0.00)		
n	124	121		
3 Min Mean (SD)	1.80 (0.89)	0.75 (0.83)	-1.05	< 0.001
5 Min Mean (SD)	2.04 (0.89)	0.88 (0.91)	-1.16	< 0.001
7 Min Mean (SD)	1.99 (0.89)	0.86 (0.91)	-1.13	< 0.001
Visit 5 (15 minute)				
n	124	120		
Pre-Challenge Mean (SD)	0.02 (0.13)	0.04 (0.32)	0.03	0.418
n	121	116		
3 Min Mean (SD)	1.72 (0.94)	0.42 (0.61)	-1.30	< 0.001
5 Min Mean (SD)	1.94 (0.91)	0.56 (0.72)	-1.38	< 0.001
7 Min Mean (SD)	1.83 (0.98)	0.59 (0.80)*	-1.24	< 0.001

Source: Module 5.3.5.1, Study CR-4484 CSR, Section 14.1, Table 6.1b.

* N=114

a Individual eye was the unit of analyses. b Difference was K-Lens minus placebo; a negative difference favors K-Lens. If data were missing within a visit, the LOCF method was used. c P value was based on two-sample t-test comparing K-Lens to placebo. NC = not calculated.
Note: At Visit 4, approximately 12 hours post-lens insertion and at Visit 5, 15 minutes post-lens insertion, the subject underwent CAC, then the subject evaluated itching on the following 0 to 4 scale: 0 = None;
0.5 = An intermittent tickle sensation possibly localized in the corner of the eye;
1.0 = An intermittent tickle sensation involving more than just the corner of the eye;
1.5 = Intermittent all-over tickling sensation;
2.0 = A mild continuous itch (could be localized) without desire to rub;
2.5 = Moderate, diffuse continuous itch with desire to rub;
3.0 = A severe itch with desire to rub;
3.5 = Severe itch improved with minimal rubbing; or
4.0 = Incapacitating itch with an irresistible urge to rub.

In order to demonstrate clinical efficacy, treatment group differences of at least 25% of the scale were demonstrated at the majority of time points evaluated. The study demonstrated clinical efficacy for K-Lens for the prevention of ocular itching.

Efficacy Summary Statement

The results of the Phase 3 conjunctival allergen challenge (CAC) studies, CR-4483 and CR-4484, were consistent, demonstrating efficacy for the prevention of itching.

Reference ID: 4943321

8. Safety

From the original Medical Officer Review dated 2/23/2022:

8.1. Safety Database

Review of the safety data focused on the Phase 3 Pool (N=804) which included data from all subjects who wore a test lens(es) at least once in at least 1 eye in the Phase 3 conjunctival antigen challenge (CAC) Studies CR-4483, CR-4484, or in the Phase 3 Studies CR-4490 and CR 4539. Pooled data from all 4 studies, provided the safety analysis set for the proposed commercial K-Lens dosage.

Across all 13 studies, 1,258 subjects were exposed to test lenses, 833 (66.2%) of whom were exposed to K-Lens 25. Of the 833 subjects exposed to K-Lens 25, 349 subjects (41.9%) wore the lenses for >60 to 91 days.

Data Excluded from Study CR-4490, Site 3

Upon review of the documentation for each clinical study, the Sponsor discovered a high number of corrections to the subject dispensing log for Site 3 from Study CR-4490 that made it difficult to ensure that subjects received the appropriate test lenses. For this reason, analyses of TEAEs and VA were performed including and excluding data from this study site for both the Phase 3 Pool and the Long-term Safety Pool.

Of the 310 randomized and treated subjects in Study CR-4490, Site 3 contributed data from 69 subjects (22.2% of the total study safety population). There were 46 subjects in the K-Lens group and 23 subjects in the placebo lens group, all of whom completed the 12-week study.

Table 8.2.1-1: Summary of Exposure to K-Lens 25 (0.019 mg/lens)
Safety Population Excluding Data from Site 3 from Study 4490 (Phase 3 Pool)

	Total (N=735)
Total Number of Subjects Exposed to K-Lens 25	490 (66.7%)
< 8 hours	1 (0.2%)
1-3 days	160 (32.7%)
> 3 – 14 days	2 (0.4%)
>14 – 30 days	5 (1.0%)
> 30 – 60 days	14 (2.9%)
> 60 -91 days	304 (62.0%)
Missing	4 (0.8%)

Source data: Module 5.3.5.3, Integrated Summary of Safety, Table TSFEXP06
Note: Percentages are based the total number of subjects exposed to K-Lens 25.
Each day of exposure is considered individually and only days that had exposure of ≥ 8 hours are counted as a day.

The safety database is considered adequate.

8.2. Deaths

There were no deaths during the clinical development of the product.

8.3. Serious Adverse Events

In the Phase 3 Pool excluding Study CR-4490, Site 3, nine subjects (0.9%) in the K-Lens 25/K-Lens 25 group experienced SAEs. These were abdominal discomfort, cholelithiasis, facial bones fracture and benign adenoma, each of which occurred in 1 subject (0.3%). No SAEs occurred in the placebo/placebo group.

8.4. Treatment Emergent Adverse Events and Adverse Reactions

Table 8.4.4-1: Incidence of Ocular Treatment Emergent Adverse Events Occurring in ≥ 1% of Subjects Safety Population Excluding Data from Site 3 from Study 4490 (Phase 3 Pool)

	K-Lens 25	Placebo
Number of Eyes in Safety Population	898	572
Total Number of Ocular Adverse Events	92	15
Number of Eyes with at Least One Ocular Adverse Event	68 (7.6%)	13 (2.3%)
Eye disorders	51 (5.7%)	8 (1.4%)
Eye irritation	14 (1.6%)	0
Eye Pain	10 (1.1%)	0
General disorders and administration site conditions	16 (1.8%)	2 (0.3%)
Instillation site pain	12 (1.3%)	1 (0.2%)

Note: Percentages are based on the number of eyes in each treatment group. Adverse events are coded using MedDRA version 20.1.
Treatment emergent adverse events are defined as those events that began on or after test lens insertion post randomization.
At each level of summarization, an eye is counted once if the eye reported one or more events.
Source Data: Module 5.3.5.3; Integrated Summary of Safety, Table TSFAE048

Table 8.4.4-2: Incidence of Non-Ocular Treatment Emergent Adverse Events Occurring in ≥ 1% of Subjects Safety Population Excluding Data from Site 3 from Study 4490 (Phase 3 Pool)

	K-Lens 25/K-Lens 25 (N=408)	K-Lens 25/Placebo (N=82)	Placebo/Placebo (N=245)
Total Number of Non-Ocular Adverse Events	107	11	50
Number of Eyes with at Least One Non-Ocular Adverse Event	77 (18.9%)	9 (11.0%)	36 (14.7%)
Infections and infestations	40 (9.8%)	0	8 (3.3%)
Nasopharyngitis	10 (2.5%)	0	2 (0.8%)
Sinusitis	9 (2.2%)	0	1 (0.4%)
Urinary Tract Infection	4 (1.0%)	0	1 (0.4%)
Respiratory, thoracic and mediastinal disorders	11 (2.7%)	7 (8.5%)	8 (3.3%)
Epistaxis	0	1 (1.2%)	0
Nasal congestion	2 (0.5%)	1 (1.2%)	2 (0.8%)
Oropharyngeal pain	3 (0.7%)	2 (2.4%)	2 (0.8%)
Respiratory tract congestion	0	1 (1.2%)	0

Rhinorrhea	0	2 (2.4%)	1 (0.4%)
Sinus congestion	0	1 (1.2%)	0
Sinus disorder	3 (0.7%)	0	3 (1.2%)
Injury, poisoning and procedural complications	11 (2.7%)	0	5 (2.0%)
Procedural pain	6 (1.5%)	0	0
Nervous system disorders	4 (1.0%)	3 (3.7%)	6 (2.4%)
Headache	2 (0.5%)	3 (3.7%)	3 (1.2%)
Vascular disorders	5 (1.2%)	0	2 (0.8%)
Hypertension	5 (1.2%)	0	2 (0.8%)

Note: Percentages are based on the number of subjects in each treatment group. Adverse events are coded using MedDRA version 20.1. Treatment emergent adverse events are defined as those events that began on or after test lens insertion post randomization. At each level of summarization, a subject is counted once if the subject reported one or more events.
Source Data: Module 5.3.5.3, Integrated Summary of Safety, Table TSFAE058

8.5. Visual Acuity

Table 13: Summary of Line Changes [1] from Baseline to Last Visual Acuity Scores — Best-Corrected; Safety Population Excluding Data from Site 3 from Study 4490 (Phase 3 Pool)

	K-Lens 25	Placebo
Number of Eyes in Safety Population	898	572
Line Changes		
>= 3 Lines Increase	0	0
>= 2 to < 3 Lines Increase	0	0
>= 1 to < 2 Lines Increase	13 (1.4%)	5 (0.9%)
< 1 Line Increase or Decrease	869 (96.8%)	556 (97.2%)
>= 1 to < 2 Lines Decrease	0	0
>= 2 to < 3 Lines Decrease	0	0
>= 3 Lines Decrease	0	0
Missing	16 (1.8%)	11 (1.9%)

Note: Percentages are based on the number of eyes in each treatment group.
[1] Line change = 10 x [- log (20/dfollow-up) — (- log (20/dbaseline))], where dfollow-up is the denominator of the Snellen fraction at the last visit and dbaseline is the denominator of the Snellen fraction at baseline. A line increase (i.e., positive line change) indicates a worsening of visual acuity and a line decrease (i.e., negative line change) indicates an improvement of visual acuity.
Source Data: Mod5.3.5.3/ISS/LSFVA01

No study participants experienced clinically significant changes in visual acuity with the use of K-Lens.

Safety Summary Statement

The data contained in this original NDA establishes the safety of ACUVUE Theravision with Ketotifen (etafilcon A contact lens with ketotifen) for the correction of ametropia who are suitable for contact lens wear and experience ocular allergic itch due to allergic conjunctivitis and who do not have red eye(s) or more than 1.00 D astigmatism.

9. Advisory Committee Meeting

The application did not raise any new efficacy or safety issues. There were no issues that were thought to benefit from a discussion at an advisory committee meeting. An Advisory Committee Meeting was not held for the NDA.

10. Pediatrics

In the Phase 3 Studies CR-4490, CR-4539, CR-4483, and CR-4484, subjects as young as 8 years old were eligible for enrollment. The youngest subjects enrolled were 11 years old. Across the Phase 3 studies, 92 subjects <18 years of age were enrolled and wore at least 1 test lens for at least 1 day, of whom 63 were exposed to K-Lens 25. All but 1 subject (exposed to K-Lens 25) of the 92 pediatric subjects completed the study treatment period including 42 subjects exposed to K-Lens 25, who completed 12 weeks of treatment in the Phase 3 long-term safety studies. One pediatric subject in study CR-4539 was discontinued from the study due to a randomization error.

The safety profile (AEs or VA) for K-Lens 25 among pediatric subjects was not different from that of older subjects. No additional clinical studies are planned with K-Lens 25 in subjects younger than 11 years of age.

The applicant has requested a partial product specific waiver for pediatric individuals <11 years of age because studies are impossible or highly impracticable; there are too few pediatric patients with allergic conjunctivitis and the concomitant need for corrective vision contact lenses. The Division also agrees with the proposed assessment for pediatric individuals 11 to <18 years of age.

The product triggers PREA as a new route of administration and was presented at the Pediatric Review Committee (PeRC) on February 1, 2022. The PeRC agreed with the plan for partial waiver and assessment as described above.

11. Biostatistics

Per the original Biostatistics review finalized 1/11/22:

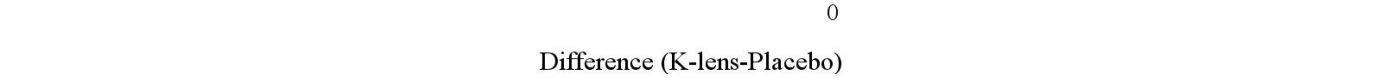
Study CR-4483 and Study CR-4484, submitted in this NDA, support the proposed indication. Both studies are multicenter, double-masked, randomized, parallel-group, placebo-controlled studies. The primary objective of these studies was to evaluate the safety and efficacy of K Lens for the prevention of ocular itching associated with allergic conjunctivitis. The studies were conducted using the conjunctival allergen challenge (CAC) model[1]. Under this model, each study consisted of 5 visits over an approximate 6-week period. The initial 3 visits were designed to determine the allergen exposure necessary to achieve a positive ocular allergic reaction. At Visits 4 (Day 0), subjects were randomly assigned to 1 of the 3 treatment groups: [1] placebo lens administered bilaterally (placebo lens /placebo lens), [2] K-Lens administered bilaterally (K-Lens/K-Lens), or [3] K-Lens administered contralaterally (K-Lens/placebo lens).

Note, placebo in these studies refers to etafilcon-A daily disposable contact lens without the drug component. Subjects were then rechallenged with the appropriate allergen dose 12 hours after lens insertion. At Visit 5 (Day 14), subjects received the same randomized lenses as assigned at Visit 4 and were challenged with the allergen 15 minutes after lens insertion.

The primary efficacy endpoint was the mean ocular itching score evaluated at 3, 5, and, 7 minutes post CAC at Visits 4 (Day 0) and Visit 5 (Day 14). Note, ocular itching was evaluated by the subject using a 0 to 4 scale with half-unit steps [0=none and 4=incapacitating itch with irresistible urge to rub]. This endpoint is consistent with endpoints considered for this indication in previous submissions.

The primary efficacy analysis was conducted based on all randomized subjects (the ITT population) using a 2-sample t-test. The last observed ocular itching score (LOCF) from a prior timepoint within a given visit was used to impute missing ocular itching score. Although randomization was done at the subject level, for treatment comparisons, the unit of analysis was the eye. The Applicant's findings in both studies established that compared with placebo-treated eyes, K-Lens-treated eyes achieved a statistically significant reduction in mean ocular itching score at both the onset and duration of action study visits (see following two tables below).

Visit (Time)	K-lens Mean (StdDev)	Placebo Mean (StdDev)	Diff(95% CI)
Day 0 (3 Min)	0.61(0.7)	1.71(0.89)	-1.1 (-1.31,-0.9)
Day 0 (5 Min)	0.74(0.73)	1.96(0.9)	-1.22 (-1.43,-1.01)
Day 0 (7 Min)	0.79(0.79)	1.86(0.94)	-1.07 (-1.29,-0.85)
Day 14 (3 Min)	0.42(0.66)	1.6(0.87)	-1.18 (-1.39,-0.98)
Day 14 (5 Min)	0.56(0.71)	1.82(0.91)	-1.26 (-1.47,-1.04)
Day 14 (7 Min)	0.54(0.7)	1.69(0.95)	-1.15 (-1.37,-0.93)



Reference ID: 4943321

Visit (Time)	K-lens Mean (StdDev)	Placebo Mean (StdDev)	Diff(95% CI)
Day 0 (3 Min)	0.75(0.83)	1.8(0.89)	-1.05 (-1.27,-0.83)
Day 0 (5 Min)	0.88(0.91)	2.04(0.88)	-1.16 (-1.38,-0.93)
Day 0 (7 Min)	0.86(0.91)	1.99(0.89)	-1.13 (-1.35,-0.9)
Day 14 (3 Min)	0.42(0.61)	1.72(0.94)	-1.3 (-1.5,-1.09)
Day 14 (5 Min)	0.56(0.72)	1.94(0.91)	-1.38 (-1.59,-1.17)
Day 14 (7 Min)	0.59(0.8)	1.83(0.98)	-1.24 (-1.47,-1.01)

Difference (K-lens-Placebo)

Both the results of the Applicant's and the reviewer's analyses of ocular itching presented provide evidence to support the efficacy of K-Lens for the treatment of ocular itching due to allergic conjunctivitis in contact lens wearers.

12. Financial Disclosure

Clinical Investigator Financial Disclosure Review Template

Application Number:	NDA 22388
Submission Date(s):	April 30, 2021
Applicant:	Johnson and Johnson Vision Care, Inc.
Product:	ACUVUE Theravision with Ketotifen (etafilcon A contact lens with ketotifen)
Reviewer:	Rhea A. Lloyd, MD
Date of Review:	August 10, 2021

Reference ID: 4943321

Covered Clinical Studies (Name and/or Number):

CR-4483
CR-4484
CR-4490
CR-4539

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of principal investigators identified: CR-4483 2 investigators, 6 sub-investigators CR-4484 6 investigators, 8 sub-investigators CR-4490 3 investigators, 16 sub-investigators CR-4539 1 investigator, 3 sub-investigators		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): CR-4483 None. CR-4484 None. CR-4490 1 investigator CR-4539 None.		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 1		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) None		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Reference ID: 4943321

From Attachment A – Form FDA 3455
DISCLOSURE: Financial Interests and Arrangements of Clinical Investigators

(b) (6) participated as a sub investigator in the below listed covered clinical study.

Covered Clinical Study: (b) (6)
A phase 3, multicenter, double-masked, randomized, parallel group, bilateral eye, placebo-controlled study to evaluate the safety and tolerability of K-Lens compared with placebo lens.
Principal Investigator: (b) (6)

Disclosure statement:
Dr. (b) (6) reported significant equity interest in the corporate parent of the sponsor, i.e., Johnson and Johnson stock valued at approximately $50,000.

Potential bias of the clinical study results for the study is mitigated by the fact that:

- The studies were double masked and involved multiple subinvestigators. In addition, the study involved multiple sites as well as multiple investigators, from which the data was pooled. Data from this study was pooled across investigators.
- Neither Vistakon Pharmaceuticals, LLC, the sponsor of the study, or its immediate parent, Johnson & Johnson Vision Care, Inc., are themselves publicly traded corporations. Potential revenue from this K-Lens product would represent only a very small portion of the Johnson & Johnson portfolio within its family of companies.

13. Study Integrity

An Office of Scientific Investigations (OSI) audit was not requested. The trials that were the focus of this application were completed between 2004 and 2009.

14. DMEPA

The Division of Medication Error Prevention and Analysis (DMEPA) finalized a review of the proposed proprietary name, Acuvue Theravision with Ketotifen, and found the proposed name conditionally acceptable on 8/24/2021.

DMEPA finalized a usability assessment and labeling review of the submitted labeling from June 1, 2021, on 12/2/2021. DMEPA determined that the proposed product is low risk and human factors data was not needed to support this NDA. Additionally, it conducted a high-level review of the submitted human factors summary reports and did not identify any use errors or difficulties of concern.

15. OPDP

The Office of Prescription Drug Promotion (OPDP) participated in labeling discussions and completed a review of the product labeling dated 2/11/2022.

16. Patient Experience Data

Regarding clinical trials CR-4483, CR-4484, CR-4490, and CR-4539:

□	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	x	Clinical outcome assessment (COA) data, such as		Sec 7. Study endpoints
		x	Patient reported outcome (PRO)	
		□	Observer reported outcome (ObsRO)	
		x	Clinician reported outcome (ClinRO)	
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify)		
□	Patient experience data that were not submitted in the application, but were considered in this review:			
		□	Input informed from participation in meetings with patient stakeholders	
		□	Patient-focused drug development or other stakeholder meeting summary reports	
		□	Observational survey studies designed to capture patient experience data	
		□	Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.			

17. Labeling

NDA 22388 ACUVUE Theravision with Ketotifen (etafilcon A drug-eluting contact lens with ketotifen) labeling submitted to the Agency on 2/24/22 and attached to the end of this review is acceptable.

18. Regulatory Action

NDA 22388 ACUVUE Theravision with Ketotifen (etafilcon A drug-eluting contact lens with ketotifen) will be approved for the prevention ocular itch due to allergic conjunctivitis and correction of refractive ametropia (myopia and hyperopia) in patients who do not have red eye(s), are suitable for contact lens wear and do not have more than 1.00 D of astigmatism.

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

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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/

WILLIAM M BOYD
02/25/2022 07:33:51 AM

WILEY A CHAMBERS
02/25/2022 08:28:46 AM