

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

022388Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 66883

**MEETING REQUEST-
WRITTEN RESPONSES**

Johnson & Johnson Vision Care, Inc.
Attention: Ms. Claudia Filauri
Regulatory Affairs Manager
500 Centurion Pkwy, Suite 100
Jacksonville, Florida 32256

Dear Ms. Filauri:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for K-Lens (etafilcon A daily disposable contact lens with ketotifen). We also refer to your submission dated January 29, 2021, containing a meeting request. The purpose of the requested meeting was to obtain concurrence from the Agency on the appropriate content and format of a New Drug Application (NDA) submission for K-Lens.

Further reference is made to our Meeting Granted letter dated February 2, 2021, wherein we agreed that written responses to your questions would be provided in lieu of a meeting. The enclosed document constitutes our written responses to the questions contained in your January 29, 2021, background package.

If you have any questions, please call Wendy Streight, PhD, Regulatory Health Project Manager at 240-405-6498.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Director
Division of Ophthalmology
Office of Specialty Medicine
Center for Drug Evaluation and Research

Enclosure:

- Written Responses

WRITTEN RESPONSES

Meeting Type: Type B
Meeting Category: Pre-NDA

Application Number: IND 66883

Product Name: etafilcon A daily disposable contact lens with ketotifen
Indication: treatment of hyperopia or myopia (vision correction);
prevention of itch associated with allergic conjunctivitis

Sponsor Name: Johnson & Johnson Vision Care, Inc.
Regulatory Pathway: 505(b)(1) of the Federal Food, Drug, and Cosmetics Act

BACKGROUND

JJVC submitted a Pre-NDA Written Response Only meeting request on January 29, 2021, to obtain concurrence from the Agency on the appropriate content and format of the NDA for K-Lens. K-Lens is a combination product that incorporates the antihistamine ketotifen fumarate into a daily disposable etafilcon A contact lens. The etafilcon A contact lenses are indicated for the correction of refractive ametropia (myopia and hyperopia) in phakic or aphakic persons with non-diseased eyes who may have 1.00 D or less of astigmatism. Ketotifen, the drug component of this combination product, is the active ingredient in the currently marketed eye drop, for the treatment of eye itching.

A Meeting Request Granted letter was sent to JJVC on February 3, 2021. The briefing package for this meeting was included in the Meeting Request on January 29, 2021.

QUESTIONS AND RESPONSES

Following, in **bold**, are the questions submitted in the January 29, 2021, meeting package. The FDA responses to these questions are in *italics*.

- 1. Does the Agency agree that the inclusion of these items will be sufficient to support the review of the K-Lens NDA?**

Proposed Table of Contents for the K-Lens NDA

- Module 1:**
 - Cover Letter
 - FDA forms
 - User Fee documents
 - Debarment Certification
 - Financial Disclosure
 - Patent information

- g. Letters of Authorization
 - h. Meeting Correspondence
 - i. Pediatric Information
 - j. Environmental Analysis
 - k. Proposed Labeling (Patient Information Guide (PIG), Package Insert and Professional Fitting and Information Guide (PI-FIG), Secondary Labeling (Carton), Primary Labeling (Lidstock) and structured product labeling (SPL))
- **Module 2:**
 - a. Quality Overall Summary
 - b. Nonclinical Overview and written and tabulated summaries
 - c. Clinical Overview
 - d. Summary of Biopharmaceutical Studies and Associated Analytical Methods
 - e. Summary of Clinical Pharmacology studies
 - f. Summary of Clinical Efficacy
 - g. Summary of Clinical Safety
 - h. Synopses of Individual Studies
- **Module 3:** Chemistry, Manufacturing, and Controls
- **Module 4:** Nonclinical Study Reports and Literature references
- **Module 5:**
 - a. Tabular listing of Clinical Studies
 - b. Clinical study reports (CSRs) and supporting documents (Synopses, Protocols, SAPs, Datasets, Listings, CRFs)
 - c. Office of Scientific Investigation Clinical Data for review (BIMO)
 - d. Literature references as needed
 - e. ISS (Discussion of the safety data for the clinical studies of K-Lens is presented in the Summary of Clinical Safety (Module 2.7.4). The Integrated Summary of Safety includes additional safety displays referenced, but not included, in the Summary of Clinical Safety.
 - f. ISE (Discussion of the efficacy data for the clinical studies of K-Lens is presented in the Summary of Clinical Efficacy (Module 2.7.3). The Integrated Summary of Efficacy includes additional efficacy displays referenced, but not included, in the Summary of Clinical Efficacy.

FDA Response: *We recommend that you include all SAS programs used to generate the datasets and the summary results that will be included in the study reports in Module 5. For us to be able to replicate your results, we request that you include detailed define files for the datasets and the SAS programs. Your proposed plan appears otherwise acceptable for filing of the application. Approval can only be determined after submission and review of the application.*

2. K-Lens clinical development program is comprised of 13 clinical studies (6 Phase 1 studies, 3 Phase 2 studies and 4 Phase 3 studies) that evaluated the relative efficacy, safety, tolerability and comfort of K-Lens in subjects with normal ocular health and in subjects with ocular allergies (seasonal allergic conjunctivitis). All studies have been completed.

Eleven (11) of which were conducted under protocols dated 01OCT2004 to 14SEP2007. During this time, the CDISC Study Tabulation Model (SDTM) standards were not adopted as they were still under evaluation. We find that while safety data related domains are well defined, the majority of the data we collect is very much contact lens specific and are not yet well defined. In 2008, SDTM data mapping was performed based on SDTM version 1.1 (SDTM IG v3.1.1) for the 11 studies. Based on a pre-NDA meeting, the 12th Study 4539 for additional safety was initiated on 19MAR2009 and due to its similarity, the database design and SDTM mappings were kept consistent with 11 prior studies. The clinical study reports (CSR) for these 12 studies are based on the 2008 SDTM datasets. In 2018, these 12 studies were converted to CDISC Study Tabulation Model (SDTM) version 1.4 (SDTM IG v3.2), (b) (4) In addition, the analysis datasets for integrated safety/efficacy were created from 2018 SDTM datasets.

JJVC intends to provide SAS version 5 transport (XPT) datasets for individual studies (all completed 13 clinical studies) in CDISC Study Tabulation Model (SDTM) version 1.4 (SDTM IG v3.2) and in the CDISC SDTM version 1.1 (SDTM IG v3.3.1) for 12 studies with CSRs completed prior to 2012. Included with the individual study datasets will be associated annotated Case Report Forms and Define in XML format for 2018 SDTM and in PDF format for 2008 SDTM respectively.

JJVC intends to provide SAS version 5 transport (XPT) data sets for integrated safety/efficacy data studies in CDISC Analysis Data Model (ADaM) version 2.1 (ADaM IG v1.1, OCCDS v1.0 and adverse event v1.0) format. Included with the integrated datasets will be the define.XML file.

Does the Agency agree with the proposed dataset submission plan described above and detailed in Table 2 List of Completed Clinical Studies and Standards?

FDA Response: *This is acceptable provided the STDM and ADaM datasets are compatible with SAS version 9.4.*

3. JJVC will perform a search of post-marketing database including Worldwide Health Organization (WHO) Adverse Drug Reaction (ADR) and FDA Adverse Event Reporting System (FAERS) for adverse events for ketotifen fumarate from FDA approval on July 2, 1999 (Zaditor® (ketotifen fumarate ophthalmic solution, 0.025%) manufactured by Ciba Vision – a Novartis company /Alcon Pharmaceuticals was originally approved under NDA 0210166 in 1999 as a prescription drug for the prevention of itching of the eye due to allergic conjunctivitis and switched to over the counter in 2006) until June 30, 2020.

The results of this search will be summarized in a separate report and datasets that will be provided in Module 5. Datasets will be provided as SAS version 5 transport (XPT) in CDISC SDTM version 1.4 (SDTM IG v3.2) and CDISC ADaM version 2.1 (ADaM IG v1.1) with the associated Define.XML v 2.0.

Does the Agency agree with this proposal?

FDA Response: *This is acceptable provided the SDTM and ADaM datasets are compatible with SAS version 9.4.*

4. K-Lens clinical development program is comprised of 13 clinical studies (6 Phase 1 studies, 3 Phase 2 studies and 4 Phase 3 studies) that evaluated the relative efficacy, safety, tolerability and comfort of K-Lens in subjects with normal ocular health and in subjects with ocular allergies (seasonal allergic conjunctivitis). All studies have been completed.

To support the Agency's inspection planning, JJVC plans to submit general study related information and specific clinical investigator information for the 4 pivotal studies (4483, 4484, 4490, 4539) (b) (4)

in tabular format as noted below:

- List of contact details of principal investigators
- Number of subjects screened per site
- Number of subjects randomized per site
- Number of subjects prematurely discontinued per site
- Location at which Sponsor trial documentation is maintained
- List of contact details of CROs
- Location at which CRO trial documentation is maintained

JJVC plans to submit this general study related information and specific clinical investigator information as pdf format.

Sample annotated CRFs and Original protocols and amendments will be provided as a cross reference to Module 5.

To support the Agency's inspection planning, JJVC also plans to submit subject level data for the 4 pivotal studies (4483, 4484, 4490, 4539) [REDACTED] (b) (4) [REDACTED] in the K-Lens NDA as a cross reference to the specific location of the information in the individual Clinical Study Reports in Module 5 as noted below:

- Listing of each subject consented/enrolled
- Subject listing for treatment assigned (randomization)
- Listing of subjects that discontinued from study treatment and list of subjects that discontinued from the study completely with date and reason discontinued
- Listing of per protocol subjects/non-per protocol subjects and reason not per protocol
- By subject listing of eligibility determination (i.e., inclusion/exclusion criteria)
- By subject listing of AEs, SAEs, deaths and dates
- By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
- By subject listing of the primary and secondary endpoint efficacy parameters or events
- By subject listing of concomitant medication
- By subject listing of testing (e.g. laboratory, ECG) performed for safety monitoring (when applicable)

Does the Agency agree with this proposal?

FDA Response: Yes.

5. JJVC plans to submit the initial agreed Pediatric Study Plan (iPSP) and a Request for Pediatric Waiver (for pediatrics under 11 years of age) with the K-Lens NDA.

Does the Agency agree with this proposal?

FDA Response: Yes.

6. There are no ongoing clinical studies with K-Lens and there will therefore be no new clinical data available within the K-Lens development program during the 4MSU reporting period for this NDA.

Additionally, K-Lens is under review in a number of countries but not yet approved in any country at this time.

In anticipation of K-Lens ex-US product launch, JJVC proposes to submit post market surveillance data in the form of medical complaints to fulfill the 4MSU

requirement, if available during the 4MSU reporting period for this NDA. The proposed date range is as follows:

- From (date of ex-US product launch) through (NDA submission +60days)

If K-Lens has not yet launched ex-US during the 4MSU reporting period for this NDA, JJVC proposes to submit a cover letter in lieu of a 4MSU.

Does the Agency agree with this proposal?

FDA Response: Yes.

Additional Comments:

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information¹ and Pregnancy and Lactation Labeling Final Rule² websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim

¹ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

² <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h³ and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*⁴. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

³ <https://www.fda.gov/media/84223/download>

⁴ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

U.S. Food and Drug Administration

Silver Spring, MD 20993

www.fda.gov

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/

WILEY A CHAMBERS
03/23/2021 05:06:45 PM



IND 066883

MEETING PRELIMINARY COMMENTS

Johnson & Johnson Vision Care, Inc.
Attention: Kelly Wilson, RAC
Project Leader II, Regulatory Affairs
7500 Centurion Parkway, Suite 100
Jacksonville, Florida 32256

Dear Ms. Wilson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for K-Lens (etafilcon A daily disposable contact lens with ketotifen).

We also refer to your March 22, 2017, correspondence received on March 23, 2017, requesting a Type C meeting to gain advice from the Agency on clinical, chemistry, manufacturing, and control, and documentation requirements for an upcoming NDA submission.

Our preliminary responses to your meeting questions are enclosed. You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

If you have any questions, please call me, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Wendy Streight, Ph.D.
Regulatory Project Manager
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

ENCLOSURE: Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: Type C
Meeting Category: Pre-NDA

Date: June 13, 2017
Time: 12:30 PM – 1:30 PM
Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Application Number: IND 066883
Product Name: K-Lens (etafilcon A daily disposable contact lens with ketotifen)
Indication: Treatment of the signs and symptoms of allergic conjunctivitis
in daily wear contact lens users
Sponsor Name: Johnson & Johnson Vision Care, Inc.

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for June 13, 2107, between Johnson & Johnson Vision Care, Inc. and the Division of Transplant and Ophthalmology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

DISCUSSION

Following, in **bold**, are the questions submitted in the May 12, 2017, meeting package. The FDA responses to these questions are in *italics*.

Product Quality

(b) (4)

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Clinical

4. **The Phase 3 clinical studies to support the efficacy and safety of K-Lens have been completed. These 4 studies were conducted with K-Lens produced on a JJVC manufacturing line in Jacksonville, FL. Commercial product will be manufactured on a JJVC manufacturing line in Limerick, Ireland. The manufacturing processes are equivalent between the 2 facilities. Given that the contact lens substrate and drug content of K-Lens will be equivalent between these 2 manufacturing lines, additional Phase 3 studies are not warranted based solely on the location of the manufacturing line. Does the Agency agree with this approach?**

FDA Response:

To bridge the products manufactured at Jacksonville, FL and Limerick, Ireland, describe any manufacturing changes to the 1-Day Acuvue contact lens since the original clinical studies were performed. Also, provide comparative product batch release results, including but not limited to, drug release data generated using a validated and acceptable drug release method. Provide details of the proposed drug release method as per the Agency recommendations previously provided in meeting minutes, May 09, 2014.

The adequacy of the submitted information is a review issue. If the bridging of the products is determined to be adequate, we do not anticipate a need for additional clinical studies.

5. **To fulfill the Medical Device Design Validation requirements of the contact lens portion of this combination product (per 21 CFR 820.30 [g]), JJVC intends to conduct an additional clinical study**

(b) (4)

a)

(b) (4)

Does the Agency agree that this approach will be adequate for the purposes of design validation?

FDA Response:

No. Refer to the response to Question 4. If the bridging of the products is determined to be adequate, we do not anticipate a need for additional clinical studies.

b) Does the Agency agree with using licensed Doctors of Optometry as Principal Investigators to evaluate the patients wearing K-Lens during the Medical Device Design Validation study?

FDA Response:

Refer to the response to Question 4. If you choose to perform an additional study for your own purposes, the qualifications of each investigator should be submitted and their qualifications will be reviewed in association with their role in the study. Please note that if the proposed study is performed, we recommend submitting a justification for the non-inferiority margins and a full statistical analysis plan with the full protocol. We may provide additional comments when the full protocol and statistical analysis plan is submitted.

6. In the NDA, JJVC intends to submit a Summary of Clinical Efficacy and Summary of Clinical Safety but not a separate Integrated Summary of Efficacy and an Integrated Summary of Safety. Does the Agency agree with this approach?

FDA Response:

Yes, your approach is acceptable.

7. JJVC used the individual eye as the unit of analysis in the Phase 3 efficacy trials. The analyses were conducted by treating the measurements from the right eye and left eye from the same subject as independent. For each Phase 3 efficacy trial, JJVC intends to supplement the planned primary efficacy analysis with a sensitivity analysis that takes into account any potential correlation between left eye score and right eye score from the same subject using a linear mixed model for repeated measures. Does the Agency agree with this approach?

FDA Response:

Yes, please provide the mathematical form of the mixed model together with a sample SAS code. Please provide an explanation in the event this analysis result differs significantly from the primary analysis result.

- 8. JJVC used Last Observation Carried Forward (LOCF) to address missing data points in the Phase 3 efficacy trials. Does the Agency agree with this approach?**

FDA Response:

Yes. We understand that the LOCF approach used post-challenge observation within the same visit only. Please discuss how you incorporated subjects with no post-challenge measure at minute 3 in a given visit in the primary efficacy analysis.

Please also conduct sensitivity analyses using methods that are valid under different missing data mechanism (Missing at random (MAR), missing not at random (MNAR)) and provide an explanation in the event the results differ.

- 9. JJVC intends to create 2 separate integrated data pools from the 4 Phase 3 trials for the Summary of Clinical Safety. There will not be an integrated data pool with all clinical data (Phase 1, 2, and 3) combined. Does the Agency agree with this approach?**

FDA Response:

Yes, the proposed approach is acceptable.

- 10. JJVC intends to provide legacy (non-granulated, except for the synopses) Clinical Study Reports (CSR) in lieu of granulated CSR's. Does the Agency agree with this approach?**

FDA Response:

Yes, the proposed approach is acceptable.

- 11. JJVC intends to cross-reference from the Module 2.7.6 Synopses of Individual Studies to Module 5.2 Tabular Listing of All Clinical Studies, and link to the CSR synopses from the Module 5.2 document. Does the Agency agree with this approach?**

FDA Response:

Yes, the proposed approach is acceptable.

Additional CMC comment:

Please provide a one-time study for leachable/extractable using the to-be-marketed container closure system using screening analytical methods (such as HPLC, GC etc.) on at least one primary (registration) batch through expiry. Refer to USP <1663>, <1664> for recommendations.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because none of the criteria apply at this time to your application, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#) including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) and [Pregnancy and Lactation Labeling Final Rule](#) websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note

that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

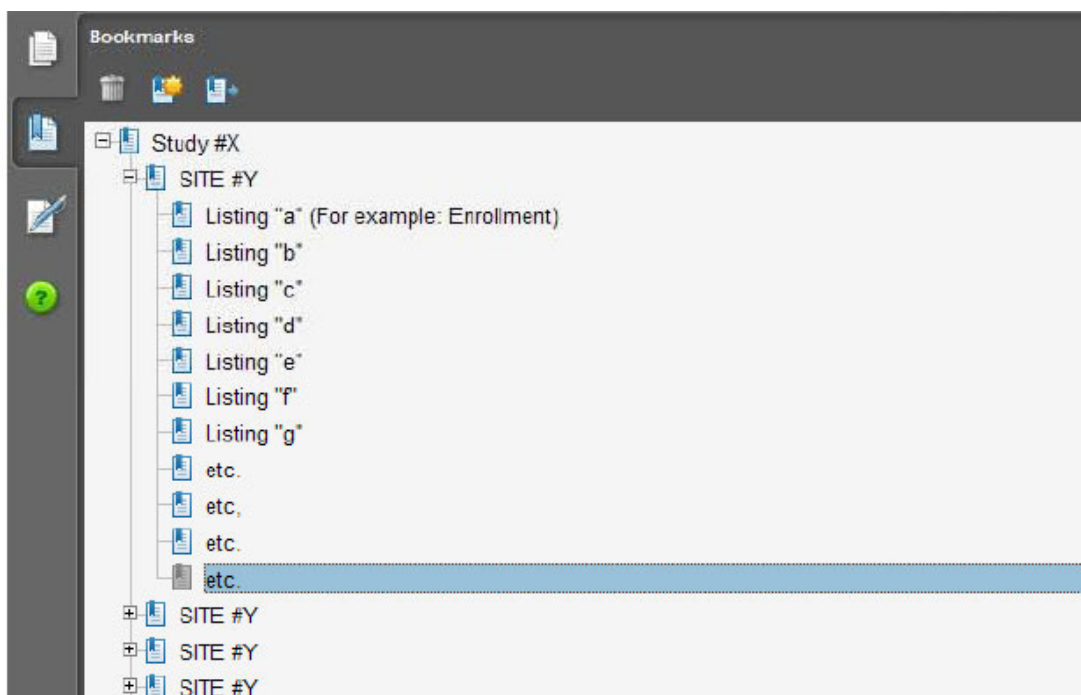
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with

respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER’s Inspection Planning” (available at the following link <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf>) for the structure and format of this data set.

Attachment 1 **Technical Instructions:** **Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format**

- A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named “BIMO [list study ID, followed by brief description of file being submitted].” In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be “bimo.” Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be “clinsite.xpt.”

DSI Pre-NDA Request Item ¹	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

- B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:



- C. It is recommended, but not required, that a Reviewer’s Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be “BIMO Reviewer Guide.” The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1

(<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>)

FDA eCTD web page

(<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm>)

For general help with eCTD submissions: ESUB@fda.hhs.gov

¹ Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WENDY M STREIGHT
06/08/2017



IND 66883

MEETING MINUTES

Ora, Inc.
Attention: Donna Welch, RN, BSN
Senior Vice President & Chief Operating Officer
300 Brickstone Square, Third Floor
Andover, MA 01810

Dear Ms. Welch:

Please refer to your Investigational New Drug Application (IND) file for K-Lens (etafilcon A daily disposable contact lens with ketotifen).

We also refer to the meeting between representatives of your firm and Ora, Inc. and the FDA on May 9, 2014. The purpose of the meeting was to discuss the characterization of the K-Lens from the new manufacture and the proposed bridging clinical study to support an NDA submission.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Christina Marshall, Regulatory Project Manager at (301) 796-3099.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, MD
Deputy Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type C
Meeting Category: Pre-NDA

Meeting Date and Time: May 9, 2014 at 10:00AM to 11:00AM
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1309
Silver Spring, Maryland 20903

Application Number: 66883
Product Name: K-Lens (etafilcon A daily disposable contact lens with ketotifen)
Indication: Treatment for correcting refractive ametropia in contact lens wearers who have 1.00D or less of astigmatism and for the prevention of itching associated with allergic conjunctivitis for up to 12 hours after lens insertion.

Sponsor/Applicant Name: Ora, Inc.

Meeting Chair: Wiley A. Chambers, MD
Meeting Recorder: Christina Marshall, MS

FDA ATTENDEES

Wiley A. Chambers, Deputy Director, Division of Transplant and Ophthalmology Products
Ozlem Belen, Safety Deputy Director
William M. Boyd, Clinical Team Leader
Rhea Lloyd, Clinical Reviewer
Yan Wang, Statistics Team Leader
Abel Eshete, Statistics Reviewer
Philip Colangelo, Clinical Pharmacology Team Leader (on phone)
Yoriko Harigaya, Clinical Pharmacology Reviewer (on phone)
Lori Kotch, Pharmacology/Toxicology Team Leader
Aaron Ruhland, Pharmacology/Toxicology Review
Balajee Shanmugam, Product Quality Reviewer
Elsbeth Chikhale, Biopharmaceutics Reviewer
John Metcalfe, Product Quality Microbiology Reviewer
Christina Marshall, Regulatory Health Project Manager
Eithu Lwin, Regulatory Health Project Manager
Judit Milstein, Chief, Project Management Staff

SPONSOR ATTENDEES

Matthew Chapin, VP, Corporate Development, Ora, Inc.
Hal Patterson, VP, Quality and CMC, Ora, Inc.
Aliza Peterson, from Johnson & Johnson
Donna Welch, RN, BSN, Senior VP, Chief Operating Officer, Ora, Inc. (on phone)
Mark B. Abelson, MD, Chief Scientific Officer, Ora, Inc. (on phone)
Jeffrey A. Coderre, PhD, Senior Manager, Regulatory Writing, Ora, Inc. (on phone)
Paul Geomes, VP, Allergy (on phone)
Nicole Kelley, Senior Regulatory Writer (on phone)
Dale Usner, PhD, VP, Biostatistics and Data Management, Statistics and Data Corporation (on phone)

BACKGROUND

Etafilcon A contact lens with ketotifen (K-Lens, IND 66,883) is intended to provide vision correction for a specific range of refractive errors while simultaneously preventing ocular itching that is associated with allergic conjunctivitis. The etafilcon A contact lens with ketotifen will allow continued contact lens use for patients experiencing ocular itching associated with allergic conjunctivitis. Ora, Inc. is proposing a change in manufacturing location from Jacksonville, FL to (b) (4) and now referred to as "K-Lens."

Ora, Inc. has requested this Type C meeting to discuss the plans for characterizing the K-Lens from the new manufacturer and the proposed bridging clinical study to support NDA submission.

For the purposes of these minutes, the questions posted by the applicant in the briefing documents are in **bold** format, the preliminary responses are in *italics* and the meeting discussions are in normal font.

DISCUSSION

Quality

(b) (4)

TOXICOLOGY

Question 4:

K-Lens incorporates ketotifen into a daily disposable etafilcon A contact lens. The safety profiles of both ketotifen fumarate ophthalmic solution, 0.025% (as contained in Zaditor[®]) and etafilcon A daily disposable contact lenses have been well established for ocular use. Ketotifen fumarate, a benzocycloheptathiophene derivative, was approved by the Food and Drug Administration (FDA) in 1999 via New Drug Application (NDA) 21-066 Zaditor[®] eye drops (ketotifen fumarate ophthalmic solution, 0.025%) for the prevention of itching due to allergic conjunctivitis. The proposed commercial product includes a single contact lens in (b) (4) of buffered ketotifen solution packaged in a blister bowl and lidstock.

Ketotifen is incorporated into etafilcon A contact lenses by packaging the lens in buffered ketotifen solution (BKS). BKS is formulated by (b) (4)

The sponsor has conducted nonclinical studies throughout the development of K-Lens as summarized in Table 8. The formulations used and their differences are presented in Table 9.

At the prior PreNDA meeting held with FDA on June 25, 2008, FDA indicated that if the preclinical studies previously reviewed were conducted adequately and the results are adequately analyzed and reports, no further studies will be required for the NDA. In addition to the existing nonclinical package, the Sponsor intends to conduct the following additional studies with product from our registration batches with K-Lenses manufactured by (b) (4) (new manufacturing site):

- Cytotoxicity
- ISO Ocular irritation (extract)
- Modified ISO Contact Lens /Solution Ocular Irritation Study following a 30-Day Lens Wear (Rabbits)
- ISO maximization sensitization studies

Does FDA agree that the above plan is acceptable to complete the nonclinical requirements to support the NDA submission for the K-Lens?

FDA Response:

From a pharmacology/toxicology perspective regarding the ketotifen component, we agree.

We agree that your proposal to conduct additional cytotoxicity, ocular irritation (extract), 30-day ocular irritation, and ISO maximization sensitizations studies is acceptable to validate the change from the (b) (4) material as well as the corresponding change in the manufacturing site.

Meeting Discussion:

None.

Clinical

Question 5:

Phase III studies CR 4490 (Appendix C) and CR 4539 (Appendix B) were conducted with the primary objective of evaluating the safety and tolerability of the proposed K-Lens formulation during 12 weeks of treatment in healthy, contact lens wearers. Both studies were very similar, utilizing a randomized, double-masked, placebo-controlled, parallel-group design. Study CR 4490 was a multi-center study, while CR 4539 was conducted at a single site. Study CR 4539 was added at the request of FDA to ensure that there were at least 300 subjects receiving at least 12 weeks of treatment with K-Lens. Note that the abridged clinical study reports have been amended and attached in Appendices B and C. In total, between the studies, 348 patients completed 12-weeks of daily dosing with K-Lens.

Does FDA agree that the combined clinical studies demonstrate the safety of K-Lens and is sufficient to support the NDA?

FDA Response:

This is a review issue and can only be addressed once the full submission has been reviewed.

Meeting Discussion:

Ora, Inc. asked if no new adverse findings were identified, would the proposed safety database be sufficient for filing of a NDA submission. The Division concurred.

Question 6:

In all 3 prior efficacy studies (one Phase II CAC, and the two Phase III CAC studies), the “eye” was the unit of analysis for the primary efficacy variables. In the proposed bridging study, the treatment will be inserted bilaterally; consequently, the unit of analysis is the average score of both study eyes. Is this approach acceptable to FDA?

FDA Response:

Agree.

Meeting Discussion:

None.

Question 7:

The briefing document includes a proposed bridging clinical study (see Appendix A for full protocol) that will evaluate the safety and the efficacy, using the conjunctival allergen challenge (CAC) method. This study will be performed with product from our registration batches (K-Lens produced at (b) (4), versus a placebo lens. Does the FDA agree that this single clinical CAC study is sufficient to bridge the manufacturing site change to complete the clinical package to support NDA submission?

FDA Response:

From a clinical perspective, a single CAC study in combination with the previously conducted studies could be sufficient to support the K-Lens produced at (b) (4). If the goal of the additional study is to be a “bridging” study, the study should include 3 arms (previous product, new product, placebo control). If the purpose of the study is to replicate the results using the “to-be-marketed” product, the study design is acceptable.

Meeting Discussion:

None.

Question 8:

Does the FDA agree that the proposed statistical approach within the enclosed protocol is sufficient for the bridging clinical CAC study?

FDA Response:

The proposed statistical approach is acceptable. Please consider the following comments:

1. The protocol states [REDACTED] (b) (4). We recommend that the worst possible itching score from the treatment group the subjects belong to be imputed for subjects with no post-challenge itching score at minute 3 in a given visit.
2. Please perform an additional sensitivity analysis by adjusting for the stratifying variable. One possible approach is to include the stratifying variable in the proposed ANCOVA model for the primary efficacy analysis.
3. Please compare the two treatment arms at each post-CAC™ challenge time point at Visits 4B and 5 with respect to the proportion of subjects with a zero itching score.

Meeting Discussion:

Ora, Inc. explained that they would prefer adjusting on the continuous measure when adjusting for baseline strata of itching. The Division agreed that this was acceptable. The Sponsor requested confirmation that the proportion of subjects with a zero itching score could be considered as a secondary endpoint. The Division concurred.

Question 9:

During Phase III studies, slight modifications were made to the buffered ketotifen solution, as shown in Table 11. It is important to note that while these changes were made to the BKS, the final drug product specifications remained unchanged. The first modification is related to [REDACTED] (b) (4) [REDACTED] (b) (4). This change did not alter release specifications. The second modification involved modifying the manufacturing procedure for the [REDACTED] (b) (4) [REDACTED] (b) (4). This change did not affect the amount of [REDACTED] (b) (4) or the final specification. The sponsor believes that these minor formulation changes did not affect the outcome of the Phase III clinical studies. Does the FDA agree?

FDA Response:

The modifications may contribute to a change. We therefore recommend conducting the planned study with the “to-be-marketed” product.

Meeting Discussion:

None.

Question 10:

Toxicokinetic evaluations of ketotifen fumarate were reported within NDA 21-066 in support of ketotifen fumarate ophthalmic solution, 0.025% and within product labeling. The distribution of ^{14}C ketotifen was studied in rabbit ocular tissues after topical administration of 50 μL of a ketotifen fumarate ophthalmic solution (0.5mg). While the cornea, bulbar conjunctiva, lower conjunctiva, and iris had high levels of radioactivity at 15 minutes, the concentrations decreased rapidly in the later time points. PK parameters were T_{max} of 1 h, $T_{1/2}$ of 1.5 h, and C_{max} of 0.087 $\mu\text{g.eq/mL}$. Plasma radioactivity was noted at 15 minutes and peaked at one hour although concentrations remained low ($< 0.1 \mu\text{g.eq/g}$) for all time points assessed. At 24 h post dosing, ketotifen was not detected in the plasma ($< 20\text{dpm}$). Comparison between single and multiple administrations of 50 μL of a ketotifen fumarate ophthalmic solution (0.5mg) showed that levels increased with the number of doses but returned to similar levels at one hour post dosing. Multiple doses only increased maximum plasma levels approximately two fold relative to a single dose. A human pharmacokinetic study was also conducted as part of a post approval commitment for ketotifen fumarate 0.025% ophthalmic solution. Fifteen healthy volunteers dosed bilaterally with ketotifen fumarate ophthalmic solution twice daily for 14 days showed plasma concentrations generally below the quantitation limit of assay ($< 20 \text{ pg/mL}$). Theoretical calculations within NDA 21-066 involving plasma concentrations associated with a 0.075 mg ophthalmic dose (assuming 100% instantaneous bioavailability) indicate that it would be highly unlikely that any drug or metabolites would be detected in the plasma.

The sponsor understands that Pharmacokinetic work is a requirement for an NDA; however, ocular pharmacokinetic (PK) work in humans is impracticable. Assuming a 50 μL dose volume, a single dose of ketotifen fumarate 0.025% ophthalmic solution contains 0.0125 mg and, based on two doses per eye per day, results in a total exposure of 0.05 mg/person /day. In comparison, for the K-Lens, each lens contains nominally 0.019 mg of ketotifen resulting in a total daily exposure per eye of 0.019 mg (0.038 mg/person/day). Assuming 100% absorption of ketotifen from K-Lens, and given that plasma concentrations in humans dosed with ketotifen fumarate ophthalmic solution, 0.025%, bilaterally twice daily for 14 days were generally below the quantitation limit of assay ($< 20 \text{ pg/mL}$), it is unlikely that any drug or metabolites would be detected in the plasma. Based on this data as well as the similarities between K-Lens and ketotifen fumarate 0.025% ophthalmic solution, negligible systemic exposure is expected with the K-Lens product. Based on the background data the sponsor believes a human PK study is not required. Does the FDA agree?

FDA Response:

Yes. We agree that no further study to assess systemic PK exposure to ketotifen following application of K-Lens (0.019 mg) is needed.

Meeting Discussion:

None.

Question 11:

Does FDA have any other comments we should consider prior to submitting NDA, which is planned for Quarter 2 2016?

FDA Response:

Subjects with greater than or equal to grade 1 corneal staining or any conjunctival redness in either eye at the baseline examination or randomization should be excluded from the study.

(b) (4)

(b) (4)

Meeting Discussion:

Ora, Inc. (b) (4)

The Division understood and agreed.

ISSUES REQUIRING FURTHER DISCUSSION

None

ACTION ITEMS

The Division will issue the minutes within 30 days.

ATTACHMENTS AND HANDOUTS

None

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILEY A CHAMBERS
05/20/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 66,883

Vistakon Pharmaceuticals, LLC
c/o Johnson & Johnson Consumer and Personal Products Worldwide
Attention: Michelle Turk
Associate Director, Regulatory Affairs
199 Grandview Road
Skillman, NJ 08558

Dear Ms. Turk:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for K-Lens (etafilcon A daily disposable contact lens with ketotifen).

We also refer to the meeting between representatives of your firm and the FDA on June 25, 2008. The purpose of the meeting was to discuss plans for an NDA for K-Lens.

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely,

{See appended electronic signature page}

Wiley Chambers, M.D.
Acting Director
Division of Anti-Infective and
Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: June 25, 2008
TIME: 12:00 PM
LOCATION: 10903 New Hampshire Avenue, Room 1419, Silver Spring, MD
APPLICATION: IND 66,883
DRUG NAME: K-Lens
TYPE OF MEETING: Pre-NDA

MEETING CHAIR: Wiley Chambers, M.D.

MEETING RECORDER: Alison Rodgers

FDA ATTENDEES:

Division of Anti-Infective and Ophthalmology Products

Wiley Chambers, MD, Acting Director
Charles Bonapace, PharmD, Clinical Pharmacology Team Leader
Conrad Chen, PhD, Pharmacology/Toxicology Reviewer
Jennifer Harris, MD, Medical Officer
Chris Kadoorie, PhD, Statistician
Lucious Lim, MD, Medical Officer
Rhea Lloyd, MD, Medical Officer
Martin Nevitt, MD, Medical Officer
Marc Robboy, Clinical Reviewer, Center for Devices and Radiological Health
Alison Rodgers, Project Manager
Wendy Schmidt, PhD, Pharmacology/Toxicology Team Leader

EXTERNAL CONSTITUENT ATTENDEES:

Vistakon Pharmaceuticals, LLC

Steve Holcroft, Vice President, Regulatory Affairs
Vsevolod Kostrubsky, PhD, Manager, Biological Sciences
Brian Pall, O.D., Principal Research Optometrist
Aliza Peterson, Vice President, Combination Products
Michelle Turk, Associate Director, Regulatory Affairs
Frank Yi, Principal Biostatistician

Consultants:

(b) (4)

BACKGROUND: On April 10, 2008, Vistakon Pharmaceuticals, LLC requested a Pre-NDA meeting. A meeting package was submitted on May 27, 2008. The Division provided responses to the questions outlined in the briefing package via email on June 23, 2008.

MEETING OBJECTIVE:

The objective of the meeting was to clarify the Division's responses to the questions outlined in the briefing package for K-Lens.

DISCUSSION:

In response to questions in the May 27, 2008, background package, the following responses were given. The format provides the firm's questions in plain lettering followed by the Agency's responses in italics. Questions, responses, and additional comments are indicated with headings.

PHARMACOLOGY/TOXICOLOGY

1. Does the Agency agree that the nonclinical studies presented in Table 3-1 are sufficient to support an NDA for (b) (4) and that no further studies are required?

Agency response: *If all the studies are conducted adequately and the results are adequately analyzed and reported, no further studies will be required for the NDA.*

NO MEETING COMMENTS

2. Does the Agency agree with the classification of nonclinical studies as proposed within Module 4 and presented in Table 3-1?

Agency response: *It appears that there is no apparent problem with classification of the non-clinical studies.*

NO MEETING COMMENTS

3. Animal line listings for the 6-month repeat dose ocular toxicity study in rabbits (Protocol CEP-T07_1548) will be provided as PDF documents as part of the toxicology report in Module 4; SAS transport files for individual animal data are not available. Please confirm that this is acceptable.

Agency response: *It is difficult to comprehend in advance in what form the study results will be submitted. Please make sure that the complete reports will be submitted to enable a thorough review by the Agency.*

MEETING COMMENTS:

- Vistakon stated that they do not have SAS transport files to submit. They asked if it would be acceptable to submit regular line listings that are not in SAS. The Division agreed that this would be acceptable. Vistakon stated that they will not include toxicokinetics because of the low systemic effects of ketotifen. The Division stated that it would be helpful to see the levels of ketotifen in the eye as well as systemically, but if the data is not available, then this would be acceptable provided there is a clean toxicology profile.

CLINICAL & STATISTICAL

4. Does the Agency agree with the classification of clinical studies as proposed within Module 5 and presented in Table 4.1-1?

Agency response:

The Division does not recognize a particular classification system for clinical studies.

MEETING COMMENTS:

- Vistakon acknowledged the Division's response.

5. Based on the completed clinical development program presented in Table 4.1-1 and the nominal maximal exposure presented in Table 4.1-2, is there adequate safety and efficacy data to support filing of the proposed (b) (4) NDA?

Agency response:

No. It is recommended that the clinical program include enough patients to identify adverse events that occur at a rate of 1% or greater. To accomplish this, it is recommended that approximately 500 or more subjects using the test drug product complete treatment with a concentration of the test drug product at least as high as proposed for marketing with a frequency at least as frequent as proposed for marketing. Prior to an NDA submission, it is recommended that at least 300 patients would have completed at least 6 weeks of follow-up after initiation of treatment.

The 12-week Safety Study CR4490 enrolled 310 subjects, 192 of these subjects were treated with K-Lens 25 (ketotifen fumarate 0.019 mg).

MEETING COMMENTS:

- Vistakon stated that they believe they have established the safety of K-Lens. Vistakon reviewed data that the Division has not yet seen:
 - (1) Laboratory data: When Ketotifen is combined into the contact lens, the properties of the lens are not changed.
 - (2) Clinical trials: Attrition and adverse event reports in patients wearing K-Lens have been low.
 - (3) Statistical rationale for why the number of patients exposed to K-Lens to date supports safety: If another 108 patients are added to the 192 already studied in order to reach 300, there is only a 0.2% difference in the ability to identify an adverse event. Vistakon has studied more than 300 patients, but the majority were exposed to K-Lens for 3 days or less.
- Vistakon asked if the Division was aware of safety concerns unknown to Vistakon. In addition, Vistakon proposed that they submit new data to support safety.
- The Division stated that Vistakon needed to detect adverse events that occur at a rate of 1% or greater; this is a requirement for all ophthalmic sponsors. The Division will review any information that Vistakon submits, but does not recommend submitting an NDA application that does not meet the recommendation above. The Division reminded Vistakon that ICH guidelines recommend that 1500 patients be studied for

different durations and doses.

- Vistakon asked if they could submit the NDA with the understanding that they would still conduct a study of 300 patients. The Division responded that this would not be acceptable.
 - Vistakon stated that when they submitted their protocol, they were asked to increase duration, but not the number of patients. The Division responded that it does not necessarily know what a sponsor is trying to accomplish at the time a protocol is submitted; the Division reviews what is submitted.
 - Vistakon asked if the Division would provide the additional number of patients that would be acceptable. The Division responded that it asks sponsors to target 500 patients so they will have 300 patients to analyze.
6. Are the data presentation strategies, as presented in the sample study report Table of Contents (see Appendix 1) and Statistical Analysis Plan (see Appendix 2 and 3), for the pivotal Phase 3 efficacy and safety trials adequate to support the NDA submission?

Agency response:

No. A tabulation of subjects who were discontinued for any reason including their case report forms should be included for all discontinued subjects as well. Note, the data analysis sets from all trials should be submitted and not just those from the Phase 3 trials.

MEETING COMMENTS:

- Vistakon stated that it would provide the information.

7. The NDA submission for (b) (4) will include a Clinical Overview and Summary (Module 2.5 and 2.7). Summaries of each efficacy study will be provided in Module 2.5.4 and 2.7.3, however no efficacy analyses combining studies is planned. The summary of safety (Module 2.5.5 and 2.7.4) will include summaries of adverse events as described in the Statistical Analysis Plan. No explicit Integrated Summary of Efficacy (ISE) or Integrated Summary of Safety (ISS) is planned. Please confirm that this acceptable.

Agency response:

Not acceptable. Efficacy analyses combining studies are not required but the NDA submission should include both an Integrated Summary of Efficacy (ISE) and an Integrated Summary of Safety (ISS).

MEETING COMMENTS:

- Vistakon requested clarification of the Division's expectations for the Integrated Summaries of Safety (ISS) and Integrated Summaries of Efficacy (ISE) in Modules 2 and 5. The Division stated that it requires these two summaries in an NDA, but does not expect separate analyses for each module.
8. Is the Statistical Analysis Plan for the Summary of Clinical Safety (see Appendix 4) acceptable, in particular, the grouping of studies and demographic stratification?

Agency response:

The primary analysis of treatment should be by eye, not by patient or treatment design (i.e., contralateral vs. bilateral).

MEETING COMMENTS:

- Vistakon confirmed their understanding of the Division's response.
9. As there were no patient deaths or treatment-related serious adverse events during the development program for [REDACTED] ^{(b) (4)} only Case Report Forms for patients discontinuing due to an adverse event during the clinical development program (n=6) will be provided in the NDA. Please confirm that this is acceptable.

Agency response:

Not acceptable. Case report forms for subjects who discontinued the study for any reason should be provided in the NDA submission.

MEETING COMMENTS:

- Vistakon agreed to provide the information required.
10. The vision correction portion of the indication will be supported by the absence of any clinically relevant changes in visual acuity in the Phase 3 trials which is consistent with the basis used to support contact lens clearance, including the predicate device (1•DAY ACUVUE® Brand Contact Lenses); see Appendix 5 for draft summary table of visual acuity scores. Does the Agency agree with this approach?

Agency response:

A summary of line changes in visual acuity from baseline to worst visual acuity scores could not be located. Please provide this information.

MEETING COMMENTS:

- Vistakon asked if it would be acceptable to submit line changes from baseline to worst case. The Division responded that this would be acceptable.
11. Are the results from the Phase 3 efficacy trials (see Section 4.2 for study summaries) sufficient to support the review of the proposed [REDACTED] ^{(b) (4)} NDA for the indication of prevention of itching of the eye associated with allergic conjunctivitis while correcting refractive ametropia (myopia and hyperopia) in persons who may have 1.00D or less of astigmatism?

Agency response:

The Phase 3 efficacy trials are sufficient to support filing the NDA. The adequacy of the trials to support the proposed indication is a review issue. The studies are not sufficient for a review of safety, however. Please refer to the response to question 5.

The Indication should state that the product is indicated for the "prevention of itching of the eye associated with allergic conjunctivitis in daily wear contact lens users ..." As topical application of the medication can be used for the same purpose in non-contact lens wearers,

and there are additional risks involved in contact lens wear, this product should not be indicated for patients who do not already use contact lenses.

MEETING COMMENTS:

- Vistakon agreed to modify the proposed Indication according to the Division's request.

PROPOSED PACKAGE INSERT

12. A proposed draft package insert for (b) (4) is provided in Appendix 6. Is the format and content of the proposed package insert for this drug/device combination product acceptable?

Agency response:

Discussions of specific product labeling are deferred until the time of NDA approval. Some general comments are provided below:



MEETING COMMENTS:

- Vistakon agreed to incorporate the Division's comments as they move forward with combination labeling.

13. In the proposed package insert for (b) (4) the adverse event section will provide adverse events as presented for 1•DAY ACUVUE and ketotifen ophthalmic solution (NDA 21-066), plus a summary of the safety profile as seen in the Phase 3 Safety Trial (CR-4490). Does FDA agree with the proposed presentation of adverse event data for the combination product?

Agency response:

As a combination product, all adverse event data from the drug product and the device will be included in product labeling. (b) (4)

This section should include device-related adverse reactions.

MEETING COMMENTS:

- Vistakon stated that their adverse event data includes all treatment emergent adverse events for the combination product. The Division asked if Vistakon could address drug-device adverse reactions. Vistakon responded that they would report adverse reactions, but would not necessarily indicate if itching and/or redness are due to the medication or device. Vistakon stated that no attempt was made to assign adverse event data to either the device or the drug. The Division stated that this would be acceptable.

14. Preliminary artwork for the (b) (4) allergy foil and carton that combines sufficient drug and device in (b) (4) or the primary and secondary packaging components is provided in Appendix 7. Acknowledging that final approval will be performed during NDA review, please provide feedback on the appropriateness of these components for a combination drug/device product.

Agency response:

Discussions of specific product labeling are deferred until the time of NDA approval. We have some concerns that the trade name, (b) (4) (b) (4)

NO MEETING COMMENTS

ELECTRONIC SUBMISSION

15. We plan to file a New Drug Application in eCTD format. We will use the toolset for the electronic publishing operations of the application used our sister company, Johnson & Johnson Pharmaceutical Research and Development (J&JPRD). J&JPRD has submitted several eCTD format NDAs in the last few years with the noted toolset. Given that we will be using J&JPRD electronic publishing tools, we do not believe it is necessary to file a pilot submission to FDA in advance of filing the NDA. Please confirm this is acceptable.

Agency response:

Acceptable. The agency recommends that you contact esub@cder.fda.gov. The submission of a "Pilot" is not application specific.

NO MEETING COMMENTS

16. We have not yet implemented eSignatures. Please confirm that scanned signatures are acceptable and that paper copies of signed documents do not need to be submitted.

Agency response:

Certain documents are required by regulations to be submitted with an original signature (e.g., FDA form 356h, FDA form 1571). These would need to be submitted in paper with original signatures if electronic signatures are not in use. Additionally, the user fee coversheet, financial disclosure forms, patent submitted and debarment forms should be submitted with the original signatures.

NO MEETING COMMENTS

17. In the eCTD, each nonclinical and clinical study report will be submitted as a single PDF. Please confirm that this is acceptable.

Agency response:

This is acceptable. However, if a submission is “illegible, uninterpretable, or otherwise clearly inadequate, including having incompatible formats or inadequate organization”, the Agency may refuse to file an application under our regulations (e.g., 21 CFR 314.101 and 601.2).

NO MEETING COMMENTS

ACTION ITEMS: None

Linked Applications

Sponsor Name

Drug Name

IND 66883

VISTAKON
PHARMACEUTICALS
LLC

VISTAKON/ZADIT(ETAFILCON/KETOTICF
EN FUMA

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILEY A CHAMBERS
07/25/2008



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 66,883

Vistakon Pharmaceuticals, LLC
Attention: Elizabeth Turek
Senior Director, Regulatory Affairs
Johnson & Johnson Consumer and Personal Products Worldwide
199 Grandview Road
Skillman, NJ 08558

Dear Ms. Turek:

Please refer to Investigational New Drug Application (IND) file for etafilcon (b) (4)
[REDACTED] Contact Lens (K-Lens).

We also refer to the meeting between representatives of your firm and the FDA on December 1, 2006. The purpose of the meeting was to discuss the Phase 3 development program.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Alison Rodgers, Regulatory Project Manager, at (301) 796-0797.

Sincerely,

{See appended electronic signature page}

Janice M. Soreth, M.D.
Director
Division of Anti-Infective and
Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

MEETING DATE: December 1, 2006
TIME: 11:00 AM
LOCATION: 10903 New Hampshire Avenue, Room 1415, Silver Spring, MD
APPLICATION: IND 66,883
DRUG NAME: etafilcon A (b) (4)
Contact Lens (K-Lens)
TYPE OF MEETING: End-of-Phase 2

MEETING CHAIR: Wiley Chambers, M.D.

MEETING RECORDER: Alison Rodgers

FDA ATTENDEES:

Division of Anti-Infective and Ophthalmology Products

Kimberly Bergman, PhD, Clinical Pharmacology Reviewer

William Boyd, MD, Clinical Team Leader

Wiley Chambers, MD, Deputy Director

Conrad Chen, PhD, Pharmacologist

Amy Ellis, PhD, Pharmacology Team Leader (Acting)

Jennifer Harris, MD, Medical Officer

Chris Khedouri, PhD, Statistical Reviewer

Lucious Lim, MD, Medical Officer

Rhea Lloyd, MD, Medical Officer

Martin Nevitt, MD, Medical Officer

Linda Ng, PhD, Chemistry Team Leader

Alison Rodgers, Project Manager

Thamban Valappil, PhD, Statistical Team Leader

Sonal Wadhwa, MD, Medical Officer

Center for Devices and Radiological Health

Gene Hilmantel, OD, MS, Acting Branch Chief, CDRH/ODE/DOED

Marc Robboy, OD, Clinical Reviewer

EXTERNAL CONSTITUENT ATTENDEES:

Vistakon

Shivkumar Mahadevan, Principal Scientist, Materials R&D

Susan Morris, Project Manager, Regulatory Submissions

Brian Pall, OD, Senior Research Optometrist

Aliza Peterson, Senior Director Combination Products

Ranganath Raja, Senior Staff Engineer & Project Lead

Kerry Sanders, Senior Staff Engineer, R&D Product & Process Commercialization

J&J Consumer & Personal Products Worldwide

Stephenie Barba, Vice President Regulatory Affairs

Elizabeth Turek, Senior Director Regulatory Affairs

(b) (4)

(b) (4)

Others

(b) (4)

BACKGROUND: Vistakon Pharmaceuticals, LLC submitted a request for an End-of-Phase 2 meeting on September 6, 2006, to discuss the Phase 3 development program for K-Lens. A meeting package was submitted on October 31, 2006. The division provided responses to the questions outlined in the briefing package via facsimile on November 27, 2006. The meeting served to clarify those responses.

MEETING OBJECTIVES:

To clarify the division's responses to the questions outlined in the briefing package for K-Lens.

DISCUSSION:

In response to questions in the October 31, 2006, background package, the following responses were given. The format provides the firm's questions in italics followed by FDA responses in plain lettering. Questions, responses, and additional comments are indicated with headings.

GENERAL

1. *A 505(b)(2) application is proposed that will reference previously reviewed and approved non-clinical and clinical data from NDA #21-066 for ketotifen fumarate ophthalmic drops (ZADITOR®). Is this submission approach acceptable?*

FDA Response: A 505(b)(2) application may be submitted provided the required patent certifications are included and reference is made to the agency's conclusions with respect to NDA 21-066.

Additional Comments:

There were no additional comments.

CHEMISTRY, MANUFACTURING AND CONTROLS

(b) (4)

PHARMACOLOGY/TOXICOLOGY

8. *Is the proposed toxicology program sufficient to support the use of (b) (4) as a packaging solution ingredient? Also see related CMC Question #3.*

FDA Response:

The proposed toxicology program appears sufficient with the exception that genotoxicity information is needed for (b) (4). To fulfill the genotoxicity testing requirements for (b) (4) please submit in vitro data for mutagenicity and clastogenicity.

Discussion:

- Vistakon stated that it has done the Ames test on K-lens extracts and could do mouse micronuclear testing on the extracts. Vistakon also noted that it has some information the FDA is requesting on genotoxicity. The Division recommended that Vistakon submit the information that they have for review..
 - The Division clarified that the sponsor needs to submit genotoxicity data with (b) (4) by itself (b) (4) to qualify it as an excipient and asked Vistakon to address mutagenicity and clastogenicity. The Division reminded Vistakon that they should choose their assays based on ICH recommendations for genotoxicity testing and what would be most appropriate for (b) (4) (e.g., cytotoxicity considerations).
 - Vistakon asked what type of dose ranging was required when assays are done. The Division recommended Vistakon follow the ICH standards for cytotoxicity.
9. *Will the Agency please provide comment on the acceptability of the following items regarding the proposed 6-month toxicity study:*
- a. *Treatment groups.*
 - b. *Bilateral design.*
 - c. *The contact lens wear time (8 hours) in this study.*

FDA Response:

The proposed design in a, b, and c appears acceptable.

Additional Comments:

There were no additional comments.

10. *To support the initiation of the 6-week Phase 3 Safety Trial, Vistakon has data from the completed 30-day Ocular Irritation Study (see Table 12) and plans to initiate the proposed 6-month toxicity study at least one month ahead of the clinical safety study. Will this be sufficient to initiate the Phase 3 Safety Trial?*

FDA Response:

If the completed 30 day rabbit ocular irritation study is adequate, the proposed timing of the six month study will be acceptable.

Only the summary of the completed 30-day ocular irritation study was submitted in the Meeting Package. Please submit the final study report for evaluation.

Discussion:

- Vistakon stated that the final study report had been submitted in February 2006. The Division responded that it would locate and review it.

11. *Is the proposed toxicology development program along with the preclinical data to be referenced in NDA #21-066 for ketotifen fumarate ophthalmic drops sufficient to support Phase 3 and NDA approval of K-Lens?*

FDA Response:

We anticipate that your proposed 6-month rabbit study with K-Lens™ and the genotoxicity data we requested for (b) (4) will support your Phase 3 clinical studies and NDA, provided these non-clinical studies are adequately conducted and in compliance with the GLP requirements.

Determination of adequacy will be made after FDA review of the final study reports.

Under 505 (b)(2), you may ask the Division to rely on our previous findings of safety for ketotifen fumarate ophthalmic drops to support your Phase 3 clinical trial and NDA submission.

Additional Meeting Comments:

There were no additional comments.

CLINICAL

12. *The following statement is proposed for inclusion in the product labeling to address the Agency's previous comment regarding the current warnings for contact lens use (i.e., to remove contact lenses if eyes are red):*

(b) (4)

Does this address the Agency's previous comment?

FDA Response: No.

(b) (4)

Discussion:

- Vistakon stated that they would use the same contraindication statement that is currently used for contact lenses.
13. *Does the Agency agree that studies conducted to date, along with the proposed safety study, will be sufficient to support the safety of K-Lens?*

FDA Response:

No. Refer to the response to Question 12.

Additional Meeting Comments:

There were no additional meeting comments.

14. *Please confirm the acceptability of the design of our pivotal Phase 3 efficacy studies including:*
- a. The dose to be evaluated.*
 - b. A 12-hour lens wear time at the Visit 4 (duration of action).*
 - c. The primary efficacy endpoints.*
 - d. Sample size calculations.*
 - e. Statistical analysis plan.*

FDA Response:

Refer to response to Question 12.

- (a) Only data summaries are presented. The Agency is not able to comment on the acceptability of the dose to be evaluated.
- (b) Only trial outlines are submitted. Comments will be conveyed when the full protocols are submitted.
- (c) The primary efficacy endpoints are acceptable.
- (d) Sample size calculation is acceptable.

Additional Statistical Comments:

- i. On page 149, the second primary hypothesis appears to be misstated.
- ii. The primary analysis and the sample size estimation should be based on the same type of statistical test. It is recommended that the primary hypothesis be analyzed using a t-test with the Wilcoxon rank sum test included in a supportive analysis.
- ii. If the primary endpoint is stratified by center then randomization should also be stratified by center. Unstratified analyses should also be included for review.

- iii. Approaches to missing data should be addressed.
- iv. Note that further statistical comments will be made when the study protocol and detailed statistical analysis plan (SAP) are received.

Discussion:

- Vistakon asked for preliminary feedback regarding dose and testing for 12 hours. The Division responded that it would need to see raw scores instead of just the differences between absolute values that Vistakon provided in order to provide feedback. The Division added that it did not necessarily have safety concerns with the higher dose, and the higher dose appears to be the best dose.
- Vistakon stated that even if the drug is gone from the lens after 12 hours, they won't require that the lens be removed. The Division agreed with this plan.

15. *Does the Agency agree that the proposed Phase 3 safety trial is sufficient for NDA approval of K-Lens?*

FDA Response:

No. The Agency recommends that the safety trial be extended to 12 weeks.

Discussion:

- Vistakon stated that it would extend the safety trial to 12 weeks.

16. *Please comment on the adequacy of the overall clinical development plan to support the use of K-Lens, (b) (4) mg/lens, when administered one lens per eye per day for the prevention of itching of the eye associated with allergic conjunctivitis.*

FDA Response:

Contact lenses should be removed from red eyes throughout the clinical development plan; this would be a component of any proposed labeling.

The Division's concern that the proposed product contraindicates the current warnings for contact lens use (i.e., to remove contact lenses if eyes are red) is unchanged. Use of the proposed product would involve patients making the determination that a red eye was caused only by allergic conjunctivitis, and not a more serious condition. Placing a foreign body (contact lens) in a red eye that could have an epithelial defect would likely increase the size of an epithelial defect and introduce additional microbes thereby hastening the formation of a corneal ulcer which may not be painful in the early stages. Because the general population of patients can not reliably self diagnose the cause of a red eye, all contact lenses are contraindicated if eyes are red.

The Agency recommends that the safety trial be extended to 12 weeks.

Additional Meeting Comments:

There were no additional comments.

PEDIATRIC PLANS

17. *Will the proposed pediatric plan be sufficient to approve the use of K-Lens in patients years and older?* (b) (4)

FDA Response: There is no minimum age established in our labeling that recommends against the fitting of contact lenses. However, as soft contact lenses are designed for the adult eye, K-Lens may prove rather difficult to fit on younger patients, i.e., (b) (4), as it may either be too large to insert/ and or exhibit improper curvature.

Discussion:

- Vistakon stated that they would limit patients to (b) (4) years and older in the phase 3 trial, and asked if a waiver in children under (b) (4) would be warranted. (b) (4)

(b) (4) The Division responded that there was no reason to have exclusion criteria if the younger children can handle lenses. (b) (4)

- Vistakon asked if there was an age limit in the efficacy study. The division responded that itching normally requires at least (b) (4) year olds in order to get reliable data; there is no age limit for redness.

18. *Does the Agency agree that a waiver to exclude patients younger than (b) (4) years is warranted for K-Lens?*

FDA Response: Yes.

Additional Meeting Comments:

There were no additional comments.

DECISIONS (AGREEMENTS) REACHED:

- Vistakon will add impurity testing during stability.
- Vistakon will test high and low mass for NDA bracketing.
- Vistakon will use the same contraindication statement that is currently used for contact lenses.
- Vistakon will extend the safety trial to 12 weeks.
- Vistakon will limit patients to (b) (4) years and older in the phase 3 trial.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

None

ACTION ITEMS:

None

ATTACHMENTS/HANDOUTS:

None

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Wiley Chambers
12/13/2006 04:30:49 PM
Wiley Chambers for Janice Soreth