CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-810

OTHER REVIEW(S)

Date: July 17, 2006

From: Jeanne M. Delasko, RN, MS
Label Initiatives Specialist
Study Endpoint and Label Development (SEALD)
Office of New Drugs, CDER

Through: Laurie B. Burke, RPh
Director, SEALD

To: File: NDA 50-810

I have the following comments regarding format issues to convey to the applicant in the 74-day letter.

Highlights:

- Since there are no recent major changes, please delete this section heading. [See 21 CFR 201.56(d)(4)].

- Regarding Dosage and Administration, please include a cross-reference for your first statement (i.e., Days 1 and 2: Instill 1 drop in the affected eye(s) two times per day). [See 21 CFR 201.56(d)(3)].

- Regarding the adverse reactions reporting statement, you list a company website. Note that a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting. [See 21 CFR 201.57 (a)(11)].

Full Prescribing Information: Contents:

- Under Warnings and Precautions, you list full sentences to describe each subsection instead of headings. Please consider using short headings or titles. [Best Practices]

- For Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. However, the numbering does not change. It must read as follows:

    - 8.3 Nursing Mothers (not 8.2)
    - 8.4 Pediatric Use (not 8.3)
    - 8.5 Geriatric Use (not 8.4)

    Please fix numbering in Contents and Full Prescribing Information for Section 8. [See 21 CFR 201.56 (d)(1)].

- Regarding Nonclinical Toxicology, 13.1 should read Carcinogenesis, Mutagenesis, Impairment of Fertility. Delete the word "and." [See 21 CFR 201.56(d)(1)].

Full Prescribing Information (FPI):

- As mentioned above, please fix numbering for Section 8 (Use in Specific Populations).

- Regarding references, is this information necessary? If not, please consider removing. [See 21 CFR 201.57(c)(16)]

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/s/

Jeanne Delasko
7/19/2006 02:09:43 PM
CSO

Laurie Burke
7/19/2006 02:51:13 PM
INTERDISCIPLINARY

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications

MEMORANDUM

****Pre-Decisional Agency Information****

Date: March 23, 2007

To: Raphael Rodriguez, Regulatory Project Manager
Division of Anti-Infective and Ophthalmology Products

From: Sheila Ryan, Pharm.D.
Division of Drug Marketing, Advertising, and Communications

Subject: AzaSite (azithromycin ophthalmic solution) 1%
NDA 50-810

DDMAC has reviewed the proposed draft product labeling (PI), dated August 30, 2006, carton and container labels, dated June 28, 2006, for Azasite, and we offer the following comments. Please feel free to contact me with any questions or clarifications.

HIGHLIGHTS OF PRESCRIBING INFORMATION

Warnings and Precautions

1. *"Avoidance of contact lenses during use."*

   Would it be more appropriate to advise to avoid contact lenses "during therapy?" This would make it clearer to the reader that contact lenses should not be worn at all during the duration of treatment and not just when instilling the product into the eye. This also would be consistent with the wording in the full prescribing information.

FULL PRESCRIBING INFORMATION

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

1. Did any patients in the clinical studies discontinue the drug due to an adverse event? If yes, please include any available information in this section.

8.4 Pediatric Use

b(4)

Is this data clinically meaningful? Would it be more appropriate to explain that no major differences in safety and effectiveness were demonstrated between pediatric patients ≥ 1 year of age and adults?

12 CLINICAL PHARMACOLOGY

1. Is any information available regarding the possible development of resistance or cross-resistance to this product? If yes, we would recommend including this information in this section under a separate subheading.

12.2 Pharmacodynamics

b(4)

Is this claim supported by substantial evidence? If not, we recommend deleting, as it is speculative in tone.

13.2 NONCLINICAL TOXICOLOGY

13.2 Animal Toxicology and/or Pharmacology

1. Would it be more appropriate to entitle this section, "Animal Toxicology" since the section is only describing toxic effects found in animals?

2. The Microbiology section is included in this section and appears out of place. Please consider moving this entire section to a new subsection/subheading (e.g., 12.4 Microbiology) under the Clinical Pharmacology section of the label. In addition, please update the Contents section to reflect this new subsection.

14 CLINICAL STUDIES

14.1 Bacterial Conjunctivitis

1. Please consider deleting study identification numbers (such as C-01-401-003 and C-01-401-004) from this section.

2. Is it possible to define terms used in this section, such as Clinical Resolution (success and failure), Bacterial Eradication (success and failure) and Confirmed Clinical Diagnosis?

3. Is it possible to include demographic information for the patient populations studied?

4. Did any patients discontinue either study for any reason? If yes, please include any available information in this section.

5. *"Azasite solution was superior to vehicle on days 6-7 in patients who had confirmed clinical diagnosis of bacterial conjunctivitis. Clinical resolution was achieved in 63.1%...of patients treated with AzaSite versus 49.7%... of patients treated with vehicle.* b(4)

   Please consider deleting, "AzaSite was superior to vehicle," as it is promotional in tone an unnecessary since results of the study are included. This could be revised to state, "Clinical resolution was achieved in 63.1% .....of patients treated with vehicle who had confirmed clinical diagnosis of bacterial conjunctivitis."

   Also, please include the appropriate p-value for these results and consider deleting. b(4)

6. b(4)

   Please delete from this statement.
   Please consider revising to only include actual outcome data and p-value.

7. For both studies, was the secondary endpoint of "Bacterial Eradication" a prespecificed endpoint of these studies? We note this endpoint demonstrated a more favorable success rate than the primary endpoint. Is this endpoint clinically relevant? Is it closely related to Clinical Resolution?

   The current "Guidance for Industry—Clinical Studies Section of Labeling for Human Prescription Drug and Biologic Products—Content and Format"

recommends only including clinically meaningful endpoints. In addition, the guidance states if two endpoints are closely related, only one should be presented.

Also, the current guidance discourages the use of the terms, "Primary Endpoint" and "Secondary Endpoint."

8. If it is necessary to include the identify of the active control (tobramycin) in the label, please include a statement that no comparative claims can be based on the active controlled study and include any limitations to the comparative data in the label.

9. b(4)

Is this outcome supported by substantial evidence? Was this a pre-defined clinical endpoint of these studies? If not, we recommend deleting.

17 PATIENT COUNSELING

1. This section includes important information regarding avoiding contamination of the applicator tip with the eyes, fingers, etc. Should this information be included in another section of the label (e.g., Warnings and Precautions) to be consistent with other multi-dose ocular products?

2. This section also includes important information on the proper administration of this product. Should this information be included under the Dosage and Administration section of the label?

CARTON AND CONTAINER LABELS

1. DDMAC recommends deleting the picture of the eye from the carton label. The picture of a perfectly clear eye (with no redness, etc) overstates the efficacy of the product and makes a representation of the product.

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/s/

Sheila Ryan
3/23/2007 03:14:34 PM
DDMAC REVIEWER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: March 7, 2007

TO: Raphael Rodriguez, Title, Regulatory Project Manager
Wiley Chambers, M.D., Clinical Reviewer
Division of Anti-infective and Ophthalmic Products, HFD-520

THROUGH: Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch 2, HFD-47
Division of Scientific Investigations

FROM: Dianne Tesch, Consumer Safety Officer

SUBJECT: Evaluation of Clinical Inspections

NDA: #50-810

NME: No

APPLICANT: InSite Vision, Inc.

DRUG: azithromycin ophthalmic solution

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Treatment of bacterial conjunctivitis

CONSULTATION REQUEST DATE: July 24, 2006

DIVISION ACTION GOAL DATE: March 1, 2007

PDUFA DATE: April 28, 2007

I. BACKGROUND:

Conjunctivitis is an inflammation of the mucous membranes covering the white of the eyes and the inner side of the eyelids. It is a very common eye condition. It usually affects both eyes at the same time although it may start in one eye and spread to the other after a day or two. It may be asymmetrical, affecting one eye more than the other. There are many causes and the treatment will depend upon the cause. It is not serious but can be very uncomfortable. Research evidence shows that 64 per cent of cases bacterial conjunctivitis will clear on their own within five days. However, antibiotic eye medication does lead to increased cure rates and earlier remission.

Currently available antibiotic ophthalmic preparations for the treatment of bacterial conjunctivitis are dosed four or more times a day. AzaSite™ was developed as a long acting topical eye drop that can be dosed

twice a day initially, then one time a day thereafter. The sponsor proposes that the simplified treatment schedule will improve efficacy through better compliance.

Protocol C-01-401-003 is a randomized, double-masked, parallel clinical trial comparing azithromycin solution to Vehicle in the treatment of bacterial conjunctivitis. The primary efficacy endpoint is clinical resolution at Visit 3 (Day 6/7), defined as absence of conjunctival discharge, bulbar conjunctival injection, and palpebral conjunctival injection. Efficacy is further evaluated by bacterial eradication, or absence of growth of baseline bacteria.

Protocol C-01-401-004 is a randomized, double-masked, parallel clinical trial comparing azithromycin solution to tobramycin ophthalmic solution in the treatment of bacterial conjunctivitis. The primary efficacy endpoints are the same as for the other protocol. The clinical sites were chosen because the investigators were the highest enrollers.

NDA 50-810 azithromycin ophthalmic solution
Summary Report of U.S. Inspections

II. RESULTS (by protocol/site):

Name of CI and site #, if known	City, State	Protocol #	Insp. Date	EIR Received Date	Final Classification
Michael Tepedino	High Point, NC	C-01-401-003 C-01-401-004	12/5/06- 12/8/06	12/26/06	NAI
Eugene Protzko	Bel Air, MD	C-01-401-004	1/10/07- 1/17/07	2/5/07	NAI
InSite Vision, Inc.	Alameda, CA	C-01-401-003 C-01-401-004	1/17/07- 1/24/07	3/7/07	VAI

Key to Classifications
NAI = No deviation from regulations. Data acceptable.
VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.
VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability
OAI = Significant deviations for regulations. Data unreliable.

A. Protocol #C-01-401-003

1. Michael Tepedino, High Point, NC:

a. Fourteen subjects were randomized, and twelve completed the study. All of the records were audited.

b. There were no limitations to the inspection.

c. There were no regulatory deficiencies at this site. However, for six of the twelve records there were discrepancies between what the CI recorded in the source document and on the CRF, and what the sponsor reported to the FDA. Specifically, if conjunctivitis was present in only one eye the CI recorded "no change" in the eye signs/symptoms portion of the CRF for the eye that was not being treated. However, the data listings supplied by the sponsor read "resolved" rather than "no change".

d. The discrepancy between the sponsor supplied data listings and the source documents and CRFs found at the site referred to the untreated eye. There was no effect on data integrity. The data are acceptable for consideration in the NDA review decision.

B. Protocol #C-01-401-004

1. Michael Tepedino, High Point, NC:

   a. One hundred-one subjects were randomized and ninety-six subjects completed the study. An audit of forty-three subjects' records was conducted. For sixteen of the forty-three records there were discrepancies between what the CI recorded in the source document and on the CRF, and what the sponsor reported to the FDA. These discrepancies were the same as in Protocol C-01-401-003.

   b. There were no limitations to the inspection.

   c. There were no regulatory deficiencies at this site.

   d. The discrepancy between the sponsor supplied data listings and the source documents and CRFs found at the site referred to the untreated eye there was no effect on data integrity. The data are acceptable for consideration in the NDA review decision.

2. Eugene Protzko, Bel Air, MD:

   a. One hundred thirty four subjects were randomized. Forty-five records were reviewed for the inspection. For twelve of the forty five records reviewed there were discrepancies between what the CI recorded on the source documents and CRFs and what the sponsor supplied in the line listings.

   b. There were no limitations to the inspection.

   c. There were no regulatory deficiencies at this site.

   d. The discrepancy between the sponsor supplied data listings and the source documents and CRFs found at the site referred to the untreated eye there was no effect on data integrity. The data are acceptable for consideration in the NDA review decision.

3. InSiteVision, Inc., Alameda, CA:

   a. The sponsor inspection took place January 17-24, 2007. The sponsor was questioned specifically regarding the discrepancies between the CRFs and the sponsor supplied line listings. The sponsor speculated that since only the line listings for "Clinical Assessment" were supplied to the inspectors they might have compared "Clinical Assessment" ratings to "Global Rating" results, thus accounting for the discrepancies. After this explanation, the FDA inspector performed a data audit and did not find any discrepancies. He also verified that all data was submitted to the Agency for review prior to his inspection. The discrepancy was not cited on the Form FDA 483. The issue was not addressed in the sponsor's response letter dated February 12, 2007. Since the discrepancies all involved the untreated eye it is unlikely that there was an effect on data integrity.

   b. There were no limitations to the inspection.

   c. There were two regulatory deficiencies at the site that did not have an effect on data integrity.

   d. The data are considered acceptable.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

The study appears to have been adequately conducted. There was a persistent problem at both study sites with the non-study eye being described as cured rather than no change on the global assessment rating CRF. The errors pertained to the non-study eye and did not have an effect on data integrity.

{See appended electronic signature page}

GCPB Reviewer Name
Title

CONCURRENCE:

Supervisory comments

{See appended electronic signature page}

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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/s/

Leslie Ball
3/12/2007 02:07:46 PM
MEDICAL OFFICER