

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206911Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA 206911

SUPPL N/A

HFD-590

Trade Name **BromSite**

Generic Name **bromfenac sodium sesquihydrate**

Applicant Name **InSite Vision Incorporated**

Approval Date, If Known **April 8, 2016**

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(2)

b) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

c) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 Years

d) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21664 Xibrom/Bromday
NDA# 203168 Prolensa
NDA# 20535 Duract (Withdrawn in 2010)

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

N/A YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference

to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1
Phase 3 Study C-11-303-003

Investigation #2
Phase 3 Study C-12-303-004

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

- a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1
Phase 3 Study C-11-303-003 YES NO

Investigation #2
Phase 3 Study C-12-303-004 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1

Phase 3 Study C-11-303-003

YES

NO

Investigation #2

Phase 3 Study C-12-303-004

YES

NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1

Phase 3 Study C-11-303-003

Investigation #2

Phase 3 Study C-12-303-004

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 – C-11-303-003

IND 107723 **YES X** NO
Explain:

Investigation #2 – C-12-303-004

IND 107723 **YES X** NO
Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

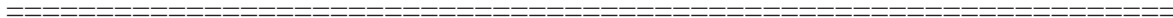
Investigation #1 !
 !
YES ! NO
Explain: ! Explain:

Investigation #2 !
 !
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES **NO X**

If yes, explain:



Name of person completing form: Diana Willard
Title: Chief, Project Management Staff
Date: March 17, 2016

Name of Office/Division Director signing form: Renata Albrecht, M.D.
Title: Director, Division of Transplant and Ophthalmology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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/s/

DIANA M WILLARD
04/11/2016

RENATA ALBRECHT
04/11/2016

Dear Dr. Hosseini,

In order to continue with the timely review of your June 10, 2015, submission of NDA 206911/ ISV-303 (0.075% bromfenac ophthalmic solution), we request that you provide the following information by January 7, 2016.

Please confirm that the protocols for Study C-11-303-003 and C-11-303-004 were identical. If there were any differences in study design, inclusion/exclusion criteria, study schedule, etc. between the protocols, please identify them.

If you have any questions regarding this communication, please contact me at (301) 796-0763.

Sincerely,

Judit Milstein on behalf of Diana Willard
Chief, Project Management Staff
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

JUDIT R MILSTEIN

12/14/2015

NDA 206911-Clinical Information request. Judit Milstein on behalf of Diana Willard



NDA 206911

INFORMATION REQUEST

InSite Vision Incorporated
Attention: Kamran Hosseini, MD, PhD
VP, Clinical and Regulatory Affairs/Chief Medical Officer
965 Atlantic Avenue
Alameda, CA 94501

Dear Dr. Hosseini:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for BromSite (bromfenac) ophthalmic solution.

We are reviewing the Chemistry, Manufacturing, and Controls section of your submission and have the following comments and information requests. We request a prompt written response by December 10, 2015, in order to continue our evaluation of your NDA.

Process Comments:

1. [REDACTED] (b) (4)
2. Specify the [REDACTED] (b) (4) to be used during drug product manufacturing. Provide compatibility study results for the [REDACTED] (b) (4) to demonstrate that they are not additive, reactive, and absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product.
3. Discuss the criticality of the claimed [REDACTED] (b) (4) in the formulation. Indicate whether its [REDACTED] (b) (4).
4. For registration batches 00313B and 00313C, you reported actual/theoretical yield reconciliations of [REDACTED] (b) (4) %, respectively. Explain the [REDACTED] (b) (4).
5. Discuss the criticality of the [REDACTED] (b) (4). Define the target [REDACTED] (b) (4).

Drug Product Comments:

1. Specify the impurities currently identified by RRTs (at [REDACTED] (b) (4)) by their [REDACTED] (b) (4) (RRT [REDACTED] (b) (4)) and [REDACTED] (b) (4) (RRT [REDACTED] (b) (4)) in the drug product release and stability specifications.
2. The Post Approval Stability Protocol and Post Approval Commitments in your study protocol SS303-009.00P did not include accelerated testing at at 40 °C/75% RH for the first three commercial batches. We recommend that you follow ICH Q1A(R2). Amend the appropriate

NDA sections to include accelerated testing at 40 °C/25% RH out to 6 months on the first three commercial batches.

3. We acknowledge your leachable study conducted for 12 months at 25 °C as reported in section 3.2.P.2.6. Testing should continue through the end of shelf life at long term storage conditions.

If you have any questions, call me at (240) 402 -8578.

Sincerely,

Erin Andrews -A

Digitally signed by Erin Andrews -A
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Erin Andrews -A,
0.9.2342.19200300.100.1.1=2001366614
Date: 2015.11.18 12:59:00 -05'00'

LT, Erin Andrews, PharmD
Regulatory Business Process Manager (RBPM)
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research Branch



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

NDA 206911

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

InSite Vision Incorporated
965 Atlantic Avenue
Alameda, CA 94501

ATTENTION: Kamran Hosseini, MD, Ph.D.
Clinical and Regulatory Affairs, Chief Medical Officer

Dear Dr. Hosseini:

Please refer to your New Drug Application (NDA), dated and received, June 10, 2015, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Bromfenac Ophthalmic Solution, 0.075 %.

We also refer to your, correspondence, dated and received, July 20, 2015, requesting review of your proposed proprietary name, Bromsite.

We have completed our review of the proposed proprietary name, Bromsite and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your July 20, 2015, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names
(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017,
(<http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf>)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Karen Townsend, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5413. For any other information regarding this application, contact Diana Willard, Regulatory Project Manager in the Office of New Drugs, at (301) 796-0833.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

TODD D BRIDGES
10/15/2015



NDA 206911

**FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED**

InSite Vision Incorporated
Attention: Kamran Hosseini, M.D., Ph.D.
Vice President, Clinical and Regulatory Affairs
Chief Medical Officer
965 Atlantic Avenue
Alameda, CA 94501

Dear Dr. Hosseini:

Please refer to your New Drug Application (NDA) dated and received June 10, 2015, , submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for BromSite (bromfenac ophthalmic solution) 0.075%.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is April 10, 2016.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by March 10, 2016.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 [CFR 201.56\(a\) and \(d\)](#) and [201.57](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [*PLR Requirements for Prescribing Information*](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances and
- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references and the proposed package insert (PI). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft [Guidance for Industry](#) (available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf>).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, 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 your application does not meet any of these criteria, PREA does not apply.

If you have any questions, call Ms. Diana Willard, Chief, Project Management Staff, at (301) 796-1600.

Sincerely,

{See appended electronic signature page}

Renata Albrecht, M.D.
Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

RENATA ALBRECHT
08/12/2015

Dear Dr. Hosseini,

Please refer to your June 10, 2015, submission of NDA 206911/ ISV-303 (0.075% bromfenac ophthalmic solution).

We have the following requests regarding this application:

Please submit to the application a sample of the product along with the entire packaging and art work.

If possible, please submit the sample, packaging, and art work by Friday, August 21, 2015.

If you have any questions regarding this communication, please contact me at (301) 796-1600.

Sincerely,

Diana Willard
Chief, Project Management Staff
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

DIANA M WILLARD
08/07/2015

Dear Dr. Hosseini,

Please refer to your June 10, 2015, submission of NDA 206911/ ISV-303 (0.075% bromfenac ophthalmic solution).

We have the following requests regarding this application:

We cannot locate the SAS programs used to generate the secondary efficacy analyses results and safety results for the three efficacy studies (C-10-303-001, C-11-303-003, and C-11-303-004) in your NDA submission. Please submit all the SAS program codes used to produce the efficacy and safety analysis results presented in the study reports of each study (C-10-303-001, C-11-303-003, and C-11-303-004). Please also provide define documents to explain the purpose of the submitted SAS codes. These documents and the SAS codes are needed for our review of your NDA.

If you have any questions regarding this communication, please contact me at (301) 796-1600.

Sincerely,

Diana Willard
Chief, Project Management Staff
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research
Food and Drug Administration

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/s/

DIANA M WILLARD
07/31/2015



NDA 206911

NDA ACKNOWLEDGMENT

InSite Vision Incorporated
Attention: Kamran Hosseini, M.D., Ph.D.
Vice President, Clinical and Regulatory Affairs
Chief Medical Officer
965 Atlantic Avenue
Alameda, CA 94501

Dear Dr. Hosseini:

We have received your New Drug Application (NDA) submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: bromfenac 0.075% ophthalmic solution

Date of Application: June 10, 2015

Date of Receipt: June 10, 2015

Our Reference Number: NDA 206911

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 9, 2015, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Attn: Renata Albrecht, M.D.
Director
Division of Transplant and Ophthalmology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications.

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

Sincerely,

{See appended electronic signature page}

Diana Willard
Chief, Project Management Staff
Division of Transplant and Ophthalmology
Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

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/s/

DIANA M WILLARD
06/12/2015



IND 107723

MEETING MINUTES

InSite Vision Inc.
Attention: Kamran Hosseini, MD, PhD
Vice President, Clinical and Regulatory Affairs
Chief Medical Officer
965 Atlantic Avenue
Alameda, CA 94501

Dear Dr. Hosseini:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ISV-303 (bromfenac ophthalmic solution), 0.075%. We also refer to the meeting between representatives of your firm and the FDA on January 13, 2014. The purpose of the meeting was to discuss the content and format of the clinical and non-clinical section of the NDA.

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

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: January 13, 2014 at 1:00-2:00 EST
Meeting Format: Teleconference

Application Number: IND 107723
Product Name: ISV-303(bromfenac ophthalmic solution) 0.075%
Proposed Indication: Treatment of postoperative inflammation and prevention and
(b) (4) of ocular pain in patients (b) (4) cataract
surgery

Sponsor/Applicant Name: InSite Vision, Inc.

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

FDA ATTENDEES

Wiley A. Chambers, Deputy Director Transplant and Ophthalmology Products
William M. Boyd, Clinical Team Leader
Martin Nevitt, Clinical Reviewer
Rhea Lloyd, Clinical Reviewer
Yan Wang, Statistics Team Leader
Yunfan Deng, Statistics Reviewer
Lori Kotch, Pharmacology/Toxicology Team Leader
Aaron Ruhland, Pharmacology/Toxicology Reviewer
Yori Harigaya, Clinical Pharmacology Reviewer
Philip Colangelo, Clinical Pharmacology Team Leader
Christina Marshall, Regulatory Health Project Manager

SPONSOR ATTENDEES

Kamran Hosseini, Vice President, Clinical and Regulatory Affairs, Chief Medical Officer
Jill Findlay, Director, Regulatory Affairs
(b) (4), Consultant, Statistician
Betsy Soares-Maddox, Senior Regulatory Affairs Associate
Judith Hutcheson, Director, Clinical Affairs
Afshin Shafiee, Director, Preclinical Research and Development

BACKGROUND

InSite Vision, Inc. is developing a topical ophthalmic formulation of bromfenac 0.075%. This drug product, herein referred to as ISV-303, is currently intended for the treatment of post-operative inflammation, prevention, (b) (4) of ocular pain (b) (4) cataract surgery twice daily for 16 days.

Similar formulations of bromfenac have been approved; bromfenac ophthalmic solution 0.09% was approved by the FDA in March 2005 as Xibrom for the treatment of postoperative inflammation and the reduction of ocular pain in patients who have undergone cataract surgery. The same formulation under the trademark Bromday was approved in 2010 for once daily dosing for 1 day prior to cataract surgery, the day of cataract surgery, and for 14 days after cataract surgery. A 0.07% bromfenac ophthalmic solution was approved in April 2013 as Prolensa with the same dosing regimen as Bromday.

InSite Vision, Inc. has requested a pre-NDA type B meeting to discuss the content and format of the clinical and non-clinical section of the NDA. 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

Question 1:

InSite Vision has created a Target Product Profile (TPP) that will be used to generate the draft product label.

a) Is the proposed indication for ISV-303 acceptable to the Agency?

FDA Response:

*It is unlikely that the proposed indication, "indicated for the treatment of postoperative inflammation and prevention (b) (4) of ocular pain in patients (b) (4) cataract surgery," will be acceptable (b) (4).
(b) (4) Final labeling can only be determined after the review of the NDA submission.*

Meeting Discussion:

The Division stated that labeling will be reviewed once the NDA is submitted and data reviewed; (b) (4)

b) InSite has proposed the proprietary name of BromSite for ISV-303 combining the USAN prefix and company name suffix to follow the naming convention established with other approved drugs developed by InSite. Does the Agency agree, at this time, this would be an acceptable trade name?

FDA Response:

The Division of Medication Error Prevention and Analysis (DMEPA) makes proprietary name determinations after review of a submitted request. We encourage you to submit your

requests for review of your proposed proprietary name during the IND phase of your drug development program. The content requirements for such a submission can be found in the draft Guidance for Industry entitled, "Contents of a Complete Submission for the Evaluation of Proprietary Names"

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf>). Please note that such a request can be made as early as at the end of phase 2 of the IND review process.

Meeting Decision:

None

- c) Provided that the second Phase 3 clinical study, Protocol No. C-12-303-004, replicates the results from the first Phase 3 clinical study, Protocol No. C-11-303-003, are the extent and nature of the clinical safety and efficacy data adequate to support the proposed indication?**

FDA Response:

See our response to Question 1(a) regarding your proposed indication. Review of full study reports will need to be completed after the NDA is submitted. We remind you of our comments from the February 17, 2012, EOP-2 meeting:

The two Phase 3 trials would be adequate to support the proposed indication provided at the time of NDA submission at least 300 subjects would have completed at least 10 days of follow-up on the dose and concentration to be marketed after initiation of treatment.

Meeting Discussion:

None

Nonclinical

Question 2:

InSite Vision has conducted a GLP 3T3 Neutral Red Uptake phototoxicity assay with bromfenac sodium [REDACTED] ^{(b) (4)} at concentrations ranging from 68.1-1000 µg/mL. The EC50 for bromfenac sodium phototoxicity was 348.3 µg/mL with a corresponding Photo-Irritant Factor of > 2.9 and a Mean Photo Effect of 0.384. The concentrations tested were well above the anticipated ocular tissue content delivered by the planned twice a day ocular dosing of ISV-303. Does the Agency agree that additional phototoxicity testing is not needed?

FDA Response:

We agree that no further photosafety testing is needed; however a general assessment of ocular phototoxicity potential should be included in the NDA application. Since there currently are no in vitro models that specifically assess ocular phototoxicity, a weight of evidence based approach is generally used to assess potential for ocular phototoxicity. Please provide the full absorption spectrum for ISV-303. For compounds that absorb at relevant wavelengths (290 and

700 nm), have a Molar Extinction Coefficient (MEC) value greater than $1000 \text{ L mol}^{-1} \text{ cm}^{-1}$, and are given via ocular routes, an overall assessment of the phototoxicity potential should be provided. Relevant nonclinical and clinical data should be discussed. Biodistribution of drug in the eye and optical properties of the eye should be considered. Any available information on the compound or chemical class-related compounds should also be considered in the overall assessment.

Meeting Discussion:
None

Question 3

InSite Vision will be submitting the NDA as a 505(b) (2) application referencing the Agency's finding of safety and effectiveness of Bromday™ (Xibrom NDA 21-664; ISTA Pharmaceuticals, Irvine, CA). InSite intends to fulfill the nonclinical requirements for the ISV-303 NDA by relying on the ocular nonclinical studies conducted by InSite. (b) (4)

a) Is the nonclinical plan as outlined in the Table 1 acceptable?

FDA Response:

(b) (4)
is not acceptable.

(b) (4)
. If you intend to rely on FDA's general finding of safety and effectiveness for a listed drug (e.g. Bromday™/Xibrom), you must establish that such reliance is scientifically appropriate. Accordingly, submit comparative PK data. If the systemic exposure level of bromfenac post ocular ISV-303 dosing is comparable or less than that of Bromday™ at the approved dose, then reliance on the Agency's finding of safety and effectiveness for Bromday may be considered scientifically justified.

Meeting Discussion:

InSite stated that they plan to rely on the FDA's general findings of safety and effectiveness of the listed drug (Bromday/Xibrom; NDA 21-664), and will submit nonclinical PK data from rabbits which demonstrates that the systemic exposure level of bromfenac post-ocular ISV-303 dosing is comparable or less than that of Bromday in the NDA. The Division responded that it agrees with the plan.

b) We plan to provide an in-depth discussion of the ocular pharmacokinetic and toxicology studies conducted with ISV-303 or bromfenac sodium sesquihydrate by InSite Vision and a (b) (4)

(b) (4) along with summaries of key relevant publications. Is this acceptable?

FDA Response:

See our response to 3(a). (b) (4)

. Pending review of your comparative PK data; however, reliance on the Agency's general finding of safety and effectiveness for Xibrom may be appropriate. Please provide a summary of comparative PK data to establish that such reliance is scientifically justified. We have the following comments regarding submission of published literature:

- Only published literature considered necessary for approval should be submitted to the application, and these data should be included in the integrated summary (e.g. Module 2).
- The integrated summary should be organized to address each of the recommended nonclinical elements (e.g. pharmacology, pharmacokinetics, general and ocular toxicity, genotoxicity, reproductive toxicity, carcinogenicity, etc.) and if literature is being relied upon to fulfill these elements, these data should be adequately summarized within the appropriate subsections of the integrated summary. A copy of each cited article should be provided. Please note that review articles should not solely be relied upon to support an application; the source articles which contain full study data should be provided.
- Published data is viewed at the same level of scrutiny as original data and expected to be of comparable/sufficient quality to support an NDA. In your integrated nonclinical summary, provide discussion of the potential impact of study shortcomings (e.g. insufficient animal numbers, insufficient endpoint analyses, formulation differences, inadequate test article characterization, etc.), if applicable.
- We encourage you to identify any listed drug(s) described in the published literature [e.g. any trade name(s)].

Meeting Discussion:

InSite Vision will provide tabulated data from both the literature and their own studies to support the NDA. The Division agreed.

- c) **Does the Agency agree that pharmacokinetic and toxicology tabulated summaries are needed only for the studies conducted by InSite Vision using ISV-303 or bromfenac sodium sesquihydrate and not for those studies reported in the Bromday (Xibrom) NDA?**

FDA Response:

Published literature provided to support the NDA (e.g., relevant Bromday/Xibrom articles) should be adequately summarized; key datasets can be provided in tabulated format, as

appropriate. Datasets obtained via SBA or FDA discipline reviews are not considered primary evidence since the original dataset is not included. (AMR)

Meeting Discussion:
None

Question 4

The pharmacokinetic and toxicology studies InSite Vision conducted with ISV-303 will be submitted as legacy reports; no Study Data Tabulation Model (SDTM) data will be provided in the NDA. Is this acceptable?

FDA Response:
Yes.

Meeting Discussion:
None

Question 5

InSite intends to use mg/kg for systemic toxicology studies to calculate the safety margin of ocular dosing as compared to oral dosing. Does the Agency agree?

FDA Response:
No. It is preferable to provide exposure multiples based on systemic AUC data rather than dose multiples based on mg/kg scaling for labeling purposes. If adequate pharmacokinetic/toxicokinetic data are available, please calculate exposure multiples based on systemic AUC data in nonclinical label sections, and provide the datasets used to make these calculations. If systemic AUC data are not available, but other estimates of systemic exposure are available, it is recommended that all available data be used to estimate systemic exposure and that the package insert describe the method used to estimate the exposure multiple along with any relevant non-clinical findings. The data and assumptions used to estimate systemic exposure should be submitted.

Meeting Discussion:
InSite explained that they were unable to provide calculations based on AUC because AUC values for oral administration are not published. InSite therefore proposed to use mg/kg. The Division suggested that InSite review the current bromfenac ophthalmic solution labeling. Final labeling will be a review issue that will be addressed after review of the submission.

Clinical

Question 6

InSite Vision intends to include the Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE) in Module 2 with corresponding datasets supplied in Module 5 as the total number of pages for Module 2.7 is expected to be less than 400. Is this acceptable?

FDA Response:
Acceptable.

Meeting Discussion:
None

Question 7

The ISS will include all subjects who received at least 1 dose of iSV-303 in Protocols C-10-303-001, C-11-303-003, and C-12-303-004; the ISE will include all subjects in the Intent-to-Treat (ITT) population of Phase 3 Protocols C-11-303-003 and C-12-303-004.

- a) **Protocol C-11-303-002 will not be included in either the ISS or ISE as it was a clinical pharmacology study which evaluated the bromfenac sodium aqueous humor concentration following 3 doses of iSV-303 prior to cataract surgery. No ophthalmic assessments were conducted post-surgery, and although adverse events and serious adverse events were to be recorded, none were reported. Does the Agency agree that we do not need to include Protocol C-11-303-002 in the ISS or ISE?**

FDA Response:
Agree.

Meeting Discussion:
None

- b) **The iSV-303 twice a day and once a day treatment groups in Protocol C-10-303-001 will be pooled into 1 arm in the ISS. Is this acceptable?**

FDA Response:
Acceptable as long as they are reported separately in the final study report for C-10-303-001.

Meeting Discussion:
None

Question 8

Based on feedback from FDA statistical reviewers, subjects who have an ACC score >0 at Day 15 or who receive rescue medication, should be treated as failures. This information was received by InSite after the finalization of our Statistical Analysis Plan (SAP) for the first Phase 3 study (C-11-303-003). Therefore, for the Clinical Study Report for this study, post hoc analyses were conducted for the primary endpoint and selected additional secondary endpoints (Table 13) in which subjects who had an ACC score > 0 at Day 15 or who received rescue medication were treated as failures.

For the second Phase 3 study, C-12-303-004, the protocol was amended such that analyses for inflammation would treat subjects who had an ACC score >0 at Day 15 or who received rescue medication would be treated as failures. Additionally, all integrated analyses for the ISE will be conducted such that subjects who had an ACC score >0 at Day 15 or who received rescue medication will be treated as failures. Is this acceptable to the Agency?

FDA Response:
Acceptable.

Meeting Discussion:
None

Question 9

As some subjects were enrolled into the Phase 3 studies but did not receive any study drug, the efficacy database will include more subjects in the ITT population than in the Safety population. Is this acceptable?

FDA Response:
Acceptable.

Meeting Discussion:
None

Question 10

 (b) (4)
Is this acceptable?

FDA Response:
No. You are reminded of our comments from the February 17, 2012 EOP-2 meeting:

It is recommended that the topical 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 10 days of follow-up after the initiation of treatment.

Meeting Discussion:

InSite Vision asked the Division to clarify that the Division was referring to 10 days of follow-up after the first dose of study drug (initiation of treatment). InSite confirmed that their Phase 3 subjects will have completed a full 16 days of follow-up after the first dose.

Question 11

Adverse events that occurred in > 5% of subjects will be summarized in the individual Phase 3 clinical study reports (Protocols C-11-303-003 and C-12-303-004). However, in the ISS, adverse events that occurred in \geq 2% of subjects will be summarized. Is this acceptable?

FDA Response:

We recommend that you summarize adverse events that occurred in \geq 1% of subjects in the ISS.

Meeting Discussion:

None

Question 12

InSite Vision will perform subgroup analyses for gender, race, and age for both the ISS and ISE. InSite has selected the following subgroup categories for age: < 65 years of age and \geq 65 years of age. Is this acceptable?

FDA Response:

Yes.

Meeting Discussion:

None

Question 13

Does the Agency require a formal statistical evaluation of homogeneous treatment response over subgroups and study sites?

FDA Response:

We do not require a formal statistical evaluation of homogeneous treatment response over subgroups and study sites. We recommend that your NDA submission includes subgroup analysis results of treatment response by age, gender, race, and study site, and provides explanations if the subgroup analysis results are not consistent with the overall primary efficacy results.

Meeting Discussion:

InSite proposed

(b) (4)

. The Division did not agree with this approach and explained that the subgroup analysis should be conducted by study site. InSite proposed to pool the small study sites, the division recommended pooling sites with 6 patients or less.

Question 14

Is the example table shell summarizing subject disposition acceptable for inclusion in the ISE and ISS, and does the Agency have any comments on the other example table shells for the ISE and ISS?

FDA Response:

The table shell (Table 1.1.1) summarizing subject disposition is acceptable. We expect that this table will also be provided for each individual study.

Meeting Discussion:

None

Question 15

Potential drug-drug and drug-disease interactions were not studied for ISV-303. (b) (4)

[REDACTED]

Is the Agency in agreement with this statement?

FDA Response:

(b) (4) *is a review issue and would only be determined at the time of the NDA review.*

Meeting Discussion:

InSite Vision asked if the Division agreed that specific drug-drug and drug-disease analyses are not needed to support the NDA. The Division agreed.

Question 16

InSite Vision intends to submit the summary level clinical site dataset within the NDA. Is this acceptable?

FDA Response:

Acceptable.

Meeting Discussion:

None

Question 17

InSite Vision proposes to control Type 1 error in our primary and secondary outcomes by using a serial gatekeeping procedure for the ISE. Is this acceptable?

FDA Response:

The proposed approach is acceptable.

Meeting Discussion:

None

Question 18

If a different procedure for multiple imputation of missing data is used in the ISE from that used in the Phase 3 studies, is this acceptable?

FDA Response:

Acceptable. We recommend that you clearly explain the rationale for choosing a different procedure for multiple imputations in the ISE.

Meeting Discussion:

None

Question 19

Raw datasets and analysis datasets will be submitted for all 4 studies in Submission Data Standards (SDS) compliant format, with the exception of Study C-10-303-001, as the analysis datasets are not available for this study. Additionally, Study data for the C-10-303-001, C-11-303-003, and C-12-303-004 will be provided in the Study Data Tabulation Model (SDTM) format, specifically SDTM v1.2 and SDTM IG v3.1.2. Is this acceptable?

FDA Response:

Your proposal is acceptable. In your analysis dataset for the ACC data, please include two flag variables: one to indicate whether a subject has received rescue medication by a given visit, and one to indicate whether a subject has missing ACC data at a given visit. We also recommend that you submit all the SAS programs codes used to derive the analysis datasets and to generate the study results for the individual studies and for the ISE and ISS.

Meeting Discussion:

None

Question 20

InSite recently discovered that a number of subjects included in the Intent-to-Treat (ITT) population of the Phase 3 studies, Protocol Nos. C-11-303-003 and C-12-303-004 did not undergo their planned cataract surgery. InSite proposes to define a modified ITT (mITT) population that will include only those subjects who were randomized into the study and underwent cataract surgery. The mITT population will be used when determining the primary and secondary efficacy endpoints, and the additional secondary efficacy analyses. This would be a change in the planned analysis for both Phase 3 studies, Protocol Nos. C-11-303-003 and C-12-303-004, but would be prospectively outlined in the integrated summary of efficacy statistical analysis plan. Does the Agency agree with this proposal?

FDA Response:

The proposal appears acceptable. In addition, we recommend you analyze the primary and secondary endpoints using subjects who were randomized into the study, underwent cataract surgery, and had at least one dose of the study treatment for both Phase 3 studies and the ISE.

Meeting Discussion:

InSite Vision proposes to define the mITT population as subjects who were randomized into the study, underwent cataract surgery, and had at least one dose of the study treatment. The Division agreed with the mITT population definition, but expects that the NDA submission to include all randomized subjects' data regardless a subjects' surgery treatment status. In addition, the Division requested that the analysis dataset include a flag variable for whether a subject had surgery or not and a flag variable for whether a subject had at least one dose of the study treatment or not.

Additional Agency Comments:

- 1) *As discussed in the February 17, 2012, EOP-2 meeting, if subjects less than 18 years old are to be excluded from the Phase 3 trials then a justification should be provided. The Phase 3 trial C-11-303-003 has been completed and only subjects > 18 were enrolled. The ongoing Phase 3 trial C-11-303-004 is only enrolling subjects > 18 years old. You have not provided an adequate justification of why subjects less than 18 years old are excluded from your Phase 3 trials.*

Under the Food and Drug Administration Safety and Innovation Act (FDASIA), a sponsor who will be submitting an application for a drug or biological product that includes a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration is required to submit an initial Pediatric Study Plan (PSP) within 60 calendar days after the date of the end-of-Phase 2 meeting or such other time as may be agreed upon between the Secretary and the applicant (21 USC 355c(a) and (e)).

The initial PSP must include an outline of the pediatric study or studies that the applicant plans to conduct (including, to the extent practicable, study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation (21 USC 355c(e)(2)(B)).

- 2) *For the analyses of primary and secondary endpoints in ISE, we recommend you use Cochran-Mantel-Haenszel test stratified by study to compare treatment difference.*

Meeting Discussion:

InSite asked if the Pediatric Waiver should be resubmitted to the IND or sent in as part of the NDA filing. The Division responded that InSite should submit a pediatric study plan

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Type B

that describes their intent to request Pediatric waiver. At the time of the NDA submission, the actual Pediatric waiver should be submitted.

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
01/27/2014



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 107723

MEETING MINUTES

InSite Vision Incorporated
Attention: Kamran Hosseini, M.D., Ph.D.
Chief Medical Officer and V.P. Clinical Affairs
965 Atlantic Avenue
Alameda, CA 94501

Dear Dr. Hosseini:

Please refer to your Investigational New Drug Application (IND) file for ISV-303 (bromfenac ophthalmic solution).

We also refer to the meeting between representatives of your firm and the FDA on February 17, 2012. The purpose of the meeting was to discuss this product's development plan.

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, please call Constantine J. Markos, B.S., Pharm.D., R.Ph., Regulatory Health Project Manager, at (301) 796-3871.

Sincerely,

{See appended electronic signature page}

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

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING

DATE: February 17, 2012
TIME: 1:00 p.m. EST
APPLICATION: IND 107723
PRODUCT NAME: ISV-303 (bromfenac ophthalmic solution)
TYPE OF DISCUSSION: Type B – End-of-Phase 2
MEETING CHAIR: Wiley A. Chambers, M.D.
MEETING RECORDER: Constantine J. Markos, B.S., Pharm.D., R.Ph.

FDA/Attendees:

Division of Transplant and Ophthalmology Products (Division)

Wiley A. Chambers, M.D.	Deputy Division Director
Conrad Chen, Ph.D.	Pharmacology/Toxicology Reviewer
Philip Colangelo, Pharm.D., Ph.D.	Clinical Pharmacology Team Leader
Yoriko Harigaya, Pharm.D.	Clinical Pharmacology Reviewer
Jennifer Harris, M.D.	Clinical Reviewer
Lori E. Kotch, Ph.D.	Acting Pharmacology/Toxicology Team Leader
Constantine J. Markos, B.S., Pharm.D.	Regulatory Health Project Manager
Denise Miller, Ph.D.	Microbiology (sterility) Reviewer
Martin Nevitt, M.D., M.P.H.	Clinical Reviewer
Mushfiqur Rashid, Ph.D.	Statistical Reviewer
Balajee Shanmugam, Ph.D.	Product Quality (CMC) Team Leader
Sonal Wadhwa, M.D.	Clinical Reviewer
Yan Wang, Ph.D.	Statistical Team Leader
Andrew Yu, Ph.D.	Product Quality (CMC) Reviewer

Sponsor/Attendees:

InSite Vision Incorporated (InSite)

Kamran Hosseini, M.D., Ph.D.

(b) (4)

Chief Medical Officer/VP, Clinical & Regulatory Affairs
Regulatory Consultant

BACKGROUND

On September 15, 2011, InSite submitted an IND meeting request. On February 14, 2012, the Division provided via e-mail, responses to the questions outlined in the briefing package dated January 12, 2012.

MEETING OBJECTIVES

To discuss this product's development plan.

DISCUSSION POINTS

For the purposes of these meeting minutes, the questions posted by InSite in the briefing document are in **bold font**, the preliminary responses sent by the Division are in *italicized font*, and the meeting discussion during the meeting is in regular font.

CMC:

- InSite Vision recently submitted an update to the CMC Section on November 4, 2011 (Serial No. 0014) which described a (b) (4) change to the ISV-303 formulation. Formulation development, manufacturing information and chemical and physico-chemical stability data were submitted. Since that submission, it was found that the (b) (4) (b) (4). Prior to the Phase 3 clinical studies which will utilize this modified formulation, InSite Vision plans to submit a CMC Update with manufacturing information and supportive stability data. Does the Agency have any comments on the modified formulation?**

FDA Response:

Viscosity is an important quality attribute and therefore your revised formulation should maintain the desired viscosity over the proposed shelf-life and retain the quality of the product. While we understand that some changes are inevitable during development, please note that changes in formulation, especially in the later stages of the clinical trial may necessitate repeating at least some of the adequate and well-controlled clinical safety and efficacy studies.

Meeting Comments: There was no further discussion of this issue.

- InSite will monitor the endotoxin levels of the ISV-303 product in clinical and site registration lots and set a specification in the NDA filing. When the NDA is approved for this product, the first ten commercial lots of product will be monitored for endotoxin levels, and the specification will be revised, if necessary. Is this plan for setting the endotoxin specification acceptable to the FDA?**

FDA Response:

Setting the endotoxin specification using the results from the clinical and site registration lots is acceptable. The re-evaluation of the endotoxin specification based on the first ten commercial lots with the possible revision of the endotoxin specification would be a basis to tighten the specification; a broadening of the specification would not be recommended.

Meeting Comments: The Sponsor stated that they will be requesting a CMC meeting as a follow-up to this meeting in the near future.

3. Because of the viscous nature of the DuraSite containing products, the volume of drug product used by each subject can be variable; therefore, during the conduct of the Phase 3 clinical study, drug product containers will be returned by each subject after the completion of dosing and weighed in order to determine the amount of drug product used by subjects and the bottle hold up over the 16 day dosing period (dosing is one drop b.i.d. in study eye). We also propose to fill the bottle with approximately (b) (4) drops of product to account for potential administration difficulty plus residual for bottle hold up resulting in a total fill of (b) (4) mLs. Fill volume for Phase 3 clinical study samples will be (b) (4).

Concurrent to the Phase 3 clinical study, InSite Vision will prepare registration stability lots and utilize a fill volume of (b) (4) or a range of (b) (4). Should InSite Vision discover from the Phase 3 data that a higher fill volume is required to meet patient needs, what change in fill volume would be allowed before it would be necessary to repeat the registration stability studies?

FDA Response:

The registration stability batches should be generated with the same fill volume in the same containers generally as that in the proposed commercial batches. Fill volume change may potentially affect the water loss and other aspect of the stability study. New data should be generated should you decide to make a change in fill volume. Change of this type should be supported with a scientific rationale of the effect of the change on the stability shelf life. This subject is a review issue.

Meeting Comments: There was no further discussion of this issue.

Non-Clinical:

1. A summary of the protocol for an ongoing 29-Day toxico-kinetic study can be found in Section 6.3.2. Does the Agency have any comments on the study design?

FDA Response:

The study protocol appears adequate.

Meeting Comments: There was no further discussion of this issue.

2. A summary of non-clinical studies completed for the ISV-303 program are summarized in Section 6.0, Table 9. Table 9 outlines the overall plan for non-clinical studies to support the NDA. Once the 29-Day toxico-kinetic study is completed and the final report submitted, InSite Vision will consider the nonclinical studies conducted to date adequate to file a marketing application. Does the Agency agree?

FDA Response:

Please submit the study reports for Formulation A when completed. If Formulation B is the formulation for marketing, a 29-Day ocular toxicology study with pharmacokinetic evaluation, should be submitted for the NDA.

Meeting Comments: The Sponsor stated that the new Formulation B will be the one that will be used for marketing. The product with (b) (4) will be used for their toxicology studies, whereas, their clinical trials will use the (b) (4)-free formulation.

3. Are the non-clinical studies conducted by InSite Vision adequate to support a marketing application without reference to Xibrom's non-clinical data? If not, what non-clinical studies need to be cross referenced?

FDA Response:

Yes. Please see the response to Question 2 above.

Meeting Comments: The Division clarified that if the Sponsor wants to file their NDA application as a 505(b)(1), then they should not reference another sponsor's data and include information that they have a right to reference in support of all labeling statements.

4. The ISV-303 formulation has been modified, and a borate (b) (4) incorporated. The original ISV-303 formulation was compared with the borate (b) (4) ISV-303 formulation in a GLP non-clinical study in rabbits (Study No. S11136). A summary of the study results can be found in Section 6.2.3. Both formulations were well-tolerated and exhibited similar pharmacokinetic profiles. Does the Agency agree with this conclusion?

FDA Response:

Based on the bromfenac concentrations in aqueous humor (Study No. S11136), Formulation A and Formulation B appear similar. However, please provide a justification for not evaluating other tissues for the comparison of the two formulations.

Meeting Comments: The Sponsor was informed to provide a justification in their submission for not evaluating other tissues for comparison of the two formulations.

Clinical:

1. InSite Vision plans to conduct two independent Phase 3 clinical trials to support a marketing application for ISV-303 (0.075% bromfenac in DuraSite). The trials will be well-controlled, randomized, double-masked, safety and efficacy studies conducted under identical protocols in which ISV-303 in DuraSite will be compared to DuraSite Vehicle. The final labeling will be “indicated for the treatment of post-operative inflammation and (b) (4) of ocular pain in patients (b) (4) cataract (b) (4).”

- a. Does the Agency agree with the clinical trial design as presented in the synopsis in Section 7.4.2?

FDA Response:

When the final protocol is submitted additional comments may be provided.

We note that you obtained aqueous humor pharmacokinetic (PK) samples to evaluate bromfenac concentrations during cataract surgery in the Phase 2 study (C-11-303-002) with the previous formulation. However, blood samples were not collected to determine systemic PK exposure to bromfenac in this study. Please provide your rationale for not determining the systemic PK exposure to bromfenac for the proposed indication, either with the previous formulation in the aforementioned Phase 2 study or with the newer formulation in the proposed Phase 3 studies, and include as part of your rationale a discussion of the lower limit of assay quantification (i.e., 50 ng/mL) for bromfenac.

Meeting Comments: The Sponsor confirmed that the pharmacokinetic drug levels were taken from the aqueous humor, and thus they are not plasma drug levels. The Division explained that if the levels are not measured then the Sponsor should assume that there is 100% absorption involved with this product’s dosing.

- b. Does the Agency agree with the proposed indication for the final labeling?

FDA Response:

Labeling will need to be determined after completion of the Phase 3 studies.

Meeting Comments: The Division stated that the Sponsor would have to explain and justify why the aqueous humor was studied instead of the plasma, and also demonstrate that it shows safety and efficacy, in order to be put into this product’s labeling. Furthermore, the Sponsor can consider studying this product with an enhanced population, such as diabetics.

- c. We plan to dose ISV-303 in DuraSite and DuraSite Vehicle twice a day (b.i.d.) for a total of 16 days: the day before surgery, the day of surgery and for 14 days after surgery. Is this dosing schedule acceptable?

FDA Response:

Acceptable, although it is not clear why bid dosing was chosen when qd dosing demonstrated apparently equivalent results.

Meeting Comments: The Division explained that the patient compliance rationale should be included to explain the choice of dosing frequency (bid dosing versus qd dosing).

d. Are the study entry criteria for the Phase 3 study acceptable?

FDA Response:

The inclusion criteria in the synopsis appear acceptable, but the exclusion criteria potentially exclude patients who have already started the study. If dosing starts prior to surgery, patients should not be excluded due to findings during surgery. If subjects less than 18 years old are to be excluded from the trial then a justification should be provided.

We will review the final protocol when submitted and provide any additional comments. Final labeling content is a review decision.

Meeting Comments: There was no further discussion of this issue.

e. The primary efficacy endpoint will be the proportion of subjects with an anterior chamber cell (ACC) grade of 0 by Day 15. Does the Agency agree that this primary endpoint is acceptable to demonstrate the efficacy of ISV-303 in the treatment of post-cataract surgery inflammation? Is the scale for grading anterior chamber cell count acceptable?

FDA Response:

The primary efficacy endpoint and anterior chamber grading scale are acceptable.

Meeting Comments: There was no further discussion of this issue.

f. As a secondary efficacy endpoint, we have designated the time in days for subjects to achieve a pain score of 0. Pain will be assessed at Day 1 (the day after cataract surgery), Day 4, Day 8 and Day 15 using the Visual Analog Scale (VAS). Pain will be scored from 0 to 100 using a mark on a 100.0 mm line (0 = absent; 100 = maximum pain). Time to resolution of ocular pain will be assessed using the VAS score. Does the Agency agree with the use of the VAS measurement system and the plan to determine the secondary efficacy endpoint?

FDA Response:

Acceptable.

Meeting Comments: There was no further discussion of this issue.

- g. InSite Vision has selected a sample size of 160 subjects in the ISV-303 group and 80 subjects into the DuraSite Vehicle group for each of our Phase 3 studies. The sample size is based on both safety and efficacy considerations as well as findings from our completed Phase 1/2 study (Protocol No. C-10-303-001). Assuming that 53% of ISV-303 recipients and 28% of Vehicle recipients have an ACC grade of 0 by Day 15, a sample size of 216 subjects (144 ISV-303 and 72 Vehicle subjects) will be required to detect statistical significance for a two-sided significance (α) level of 0.05 with a power of 0.95 for Pearson's chi-square test. The goal is to have at least 150 subjects in each study for safety analysis. Thus, assuming that 95% of enrolled subjects will be evaluable for safety, this sample size was selected. Does the Agency agree that the sample size for the Phase 3 studies is sufficient to support a marketing application?

FDA Response:

- 1) *It is recommended that the topical 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 10 days of follow-up after the initiation of treatment.*
- 2) *The proposed sample size is acceptable provided there are at least 300 patients with at least 10 days follow-up.*
- 3) *It is recommended that you conduct sensitivity analyses using different methods of imputations (e.g., multiple imputations, baseline observation carried forward, worst observation carried forward, etc.) for the primary efficacy endpoint. When addressing this issue, we recommend you to consult the book, "The Prevention and Treatment of Missing Data in Clinical Trials" (authored by a panel on Handling Missing Data in Clinical Trials and National Research Council).*
- 4) *We cannot comment on the appropriateness of the secondary efficacy endpoint (time to achieve a pain score of 0) as you did not provide information about the amount of censored data that will be expected from these studies. If the censored data are substantial, the studies may not have sufficient power to detect a treatment difference in this endpoint. We recommend your sample size calculation take into account the expected censored data for this endpoint.*
- 5) *As a secondary efficacy endpoint, we recommend you calculate the proportion of subjects who achieve a pain score of 0 by treatment group, calculate the treatment difference (with a 95% confidence interval) for this endpoint at each post-baseline timepoint.*
- 6) *We may have additional comments when you submit the SAP for review.*

Meeting Comments: The Division stated that in general, the Sponsor would need two adequate and well-controlled multi-center trials for a 505(b)(1) NDA submission. In the case of a 505(b)(2) submission, one study may be sufficient with bridging information.

2. **Adverse events, best corrected visual acuity, intraocular pressure, and bio-microscopy and ophthalmoscopy findings will be assessed for safety. Additionally, objective signs of ocular inflammation, including anterior chamber flare will be assessed using a 0-4 grading scale, and photophobia will be evaluated using a VAS score. Other signs, including chemosis, bulbar conjunctival injection, ciliary injection, corneal edema, and keratic precipitates will be evaluated according to a 0-3 grading scale. Does the Agency agree with the proposed safety assessment parameters for ISV-303?**

FDA Response:

Acceptable.

Meeting Comments: There was no further discussion of this issue.

Regulatory:

1. **InSite Vision may cross-reference ocular toxicity studies and clinical studies from the Xibrom NDA as part of our marketing application. As Xibrom has been withdrawn from marketing, is it acceptable to reference information in the Xibrom Summary Basis of Approval?**
 - a. **If so, could we file a 505(b)(2) NDA?**

FDA Response:

The proposal to file a 505(b)(2) application is acceptable; the Agency would rely on its findings of safety and efficacy.

Meeting Comments: The Division clarified that if the Sponsor submits a 505(b)(2) NDA application, one can cross-reference a drug that is no longer on the market, only if that same drug was removed from the market for reasons other than safety or efficacy.

2. **InSite Vision completed a Phase 2 clinical study (Protocol No. C-11-303-002) summarized in Section 7.3. InSite Vision would like to ask the Division if the completed Phase 2 study can be considered a pivotal study.**
 - a. **If so, InSite Vision would conduct one Phase 3 trial outlined in Section 7.4.2 as the second pivotal study as the basis for approval. Does the Agency concur?**

FDA Response:

The Agency does not make a distinction between study phases as the basis of approval. Adequate and well-controlled studies may be used to support an NDA application. The dosing regimen and follow-up for Protocol C-11-303-002 are different from the currently proposed Phase 3 trials. Protocol C-11-303-02 was dosed QD for 2 days prior to surgery and the morning of cataract surgery with follow-up at day 1 only while the currently proposed Phase 3 trials are to be dosed at BID the day prior to surgery, the day of surgery and at 14 days post-op. It is unlikely that Protocol C-11-303-002 would be considered as one of the two pivotal trials though final determination can only be determined when the complete submission is provided.

Meeting Comments: There was no further discussion of this issue.

3. Aside from the topics discussed in this meeting, can the Agency provide guidance as to any additional information which would be required to support a marketing application?

FDA Response:

At this time there is no additional information that is required, though additional comments may be provided when the final complete protocol is submitted.

Meeting Comments: There was no further discussion of this issue.

Additional Statistical recommendations on standardized datasets and analysis programs included in an NDA submission:

- *You are encouraged to submit standardized datasets following the CDISC guidelines for SDTM and ADaM datasets.*
- *Provide all raw datasets, as well as analysis datasets (including all efficacy and safety variables) used to generate the results presented in your study report. In addition, provide a data definition file (in pdf format or xml format) that includes information on how efficacy variables are derived.*
- *Include the programs used for creating main efficacy analysis datasets from submitted raw datasets and the programs used for the efficacy and main safety analyses. In addition, provide a document that explains what each program is used for.*
- *Provide the analysis datasets (with definition file) and programs (with documentation) used to generate the specific analyses results contained in the ISE reports.*
- *Provide the analysis datasets (with definition file) and programs (with documentation) used to generate the inferential analyses results in the ISS reports.*
- *You can also check the FDA website to find more information about current documents and guidances.*

Link to Study Data Specifications:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf>

Constantine J. Markos, B.S., Pharm.D., R.Ph.
Regulatory Health Project Manager

Wiley A. Chambers, M.D.
Deputy Division Director

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
03/13/2012



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

PIND 107723

MEETING MINUTES

InSite Vision Incorporated
Attention: Kamran Hosseini, M.D., Ph.D.
Chief Medical Officer and Vice President Clinical Affairs
965 Atlantic Avenue
Alameda, CA 94501

Dear Dr. Hosseini:

Please refer to your Pre-Investigational New Drug Application (PIND) file for ISV-303.

Please also refer to the meeting between representatives of your firm and the FDA on April 26, 2010. The purpose of the meeting was to discuss the development plans for this product.

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 Constantine J. Markos, Pharm.D., R.Ph., Regulatory Health Project Manager at (301) 796-3871.

Sincerely,

{See appended electronic signature page}

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

Enclosure

MEMORANDUM OF MEETING MINUTES

DATE: April 26, 2010
TIME: 11:00 a.m. EST
APPLICATION: PIND 107723
PRODUCT NAME: ISV-303
TYPE OF DISCUSSION: Type B – Pre-IND
MEETING CHAIR: Wiley A. Chambers, M.D.
MEETING RECORDER: Constantine J. Markos, Pharm.D., R.Ph.

FDA/Attendees:

Division of Anti-Infective and Ophthalmology Products (DAIOP)

Kimberly Bergman, Pharm.D.	Clinical Pharmacology Reviewer
William M. Boyd, M.D.	Clinical Team Leader
Wiley A. Chambers, M.D.	Acting Division Director
Jennifer Harris, M.D.	Clinical Reviewer
Lucious Lim, M.D.	Clinical Reviewer
Rhea Lloyd, M.D.	Clinical Reviewer
Constantine J. Markos, Pharm.D.	Regulatory Health Project Manager
Martin Nevitt, M.D., M.P.H.	Clinical Reviewer
Lin Qi, Ph.D.	Product Quality (CMC) Reviewer
Mushfiqur M. Rashid, Ph.D.	Statistical Reviewer
Wendelyn J. Schmidt, Ph.D.	Pharmacology/Toxicology Team Leader
Sonal Wadhwa, M.D.	Clinical Reviewer
Yan Wang, Ph.D.	Statistical Team Leader

InSite Vision (InSite):

Kamran Hosseini, M.D., Ph.D.	Chief Medical Officer/V.P. Clinical Affairs
 (b) (4)	Regulatory Consultant

BACKGROUND:

On January 6, 2010, InSite Vision submitted a Pre-IND (PIND) meeting request. On April 20, 2010, the Division provided InSite Vision via e-mail with responses to the questions outlined in the briefing package dated March 25, 2010.

The questions from the briefing package are restated below in bold followed in italics by the comments provided by the Division to InSite Vision. The meeting comments then follow in plain text.

MEETING OBJECTIVES:

To clarify the Division's responses to the questions outlined in the briefing package.

OPENING COMMENTS:

At the start of the meeting, InSite Vision commented that they found the comments provided by the Division very helpful; however, they would like some clarification in regards to certain questions.

DISCUSSION POINTS:

CMC:

1.ISV-3 03 is packaged in low-density polyethylene bottles and dropper tips, and (b)(4) caps. The drug product is intended for storage at ambient room condition. We intend to monitor the stability of the investigational drug product at the long-term storage condition of 25°C ± 2°C/40% RH ± 5% RH and accelerated condition of 40°C ± 2°C/NMT 25% RH as per ICH Guidance for Industry Q1A(R2) for semi-permeable containers. Does the agency agree with the proposed testing conditions?

Agency Response: *Yes, the testing conditions are acceptable.*

Additional CMC comment: *Please use ICH Q3 definitions for reporting impurities. Test and acceptance criterion will be needed for endotoxin when the IND moves to an NDA.*

Meeting Comments: *There was no further discussion of this issue.*

Pre-Clinical:

1.Is the Preclinical Plan (Section 11.1, Table 14) sufficient to support NDA filing?

PIND 107723

Meeting Minutes 04-26-10

Page 3

Agency Response: *In the planned 28-day ocular toxicity study in rabbits, the toxicokinetic evaluation should be performed to study the systemic absorption of bromfenac as compared to Xibrom.*

Meeting Comments: There was no further discussion of this issue.

2. Can we refer to the systemic and ocular data from [REDACTED] (b)(4) and Xibrom (NDA# 21-664) to support the safety of ISV-303?

Agency Response: *It is not clear whether you have obtained the right to refer to NDAs [REDACTED] (b)(4) and 021664. If an application is submitted as 505(b)(2) NDA with the appropriate notifications, you could rely on either of these NDAs or published literature and conduct appropriate bridging studies to provide adequate basis for reliance upon FDA's finding of safety and effectiveness of the approved listed drugs.*

Meeting Comments: The Division clarified that it was InSite's choice of whether to obtain a right to reference the information or submit the application as a 505(b)(2) application.

3. Can the 14-day ocular toxicity study (Section 11.4.1.1.1) support the proposed phase I/II study?

Agency Response: *From the submitted summary report, it is not clear whether the 14-day ocular toxicity study was a GLP study. It is also noted that systemic toxicokinetic was not evaluated in the study. The adequacy of the study to support the proposed clinical study will be determined when it is submitted.*

Meeting Comments: InSite confirmed that their 14-day ocular toxicity study was a GLP study. They plan to perform a 28-day toxicokinetic study.

Clinical:

1. Does the agency agree with the proposed clinical program for ISV-303?

Agency Response: *Safety and efficacy is recommended to be demonstrated in at least two adequate and well-controlled, multi-center, independent trials for ISV-303. The full statistical analysis plan for the proposed Phase 1/2 study and a full protocol including statistical plan for the future Phase 3 studies should be submitted for review. When the completed clinical protocol is submitted additional comments may follow.*

Meeting Comments: InSite stated that their IND will include all of this information.

(b) (4)

?

Agency Response:

(b) (4)

Meeting Comments: InSite inquired as to what would qualify as appropriate bridging studies. The Division explained that a 28-day ocular toxicity study with a Xibrom arm would be acceptable.

Regulatory:

1. InSite is considering the option of submitting the New Drug Application (NDA) for ISV-303 under Section 505(b)(2). InSite intends to reference Xibrom (NDA#21-664) as the Listed Drug in this 505(b)(2) application.

Agency Response: *The application may be submitted under Section 505(b)(2) to support the pre-clinical and clinical filing of the NDA. ISV-303 is a new formulation of bromfenac. For the proposed indication, safety and efficacy is recommended to be demonstrated in at least two adequate and well-controlled, multi-center, independent trials.*

Meeting Comments: There was no further discussion of this issue..

a. Would the agency allow InSite to reference the clinical efficacy and safety data from the Xibrom NDA (NDA# 21-664)?

Agency Response: *The application may reference Xibrom (NDA 21-664) to support the clinical efficacy and safety for the filing of the NDA. ISV-303 is a new formulation of bromfenac. For the proposed indication safety and efficacy is recommended to be demonstrated in at least two adequate and well-controlled, multi-center, independent trials.*

Meeting Comments: There was no further discussion of this issue.

b. Would the agency accept completion of one (1) Phase 3 study as the basis to support approval of the NDA?

Agency Response: *For the proposed indication of this lower concentration, safety and efficacy is recommended to be demonstrated in at least two adequate and well-controlled, multi-center, independent trials. If the application is submitted as a 505(b)(2), then, one clinical trial may be performed. This trial would need to be a 3-arm study comparing Bromfenac 0.09% BID (as currently labeled), versus vehicle BID, versus Bromfenac 0.075% BID.*

Meeting Comments: The Division clarified that if InSite were to show superiority over Xibrom in Phase 3 studies, they would need to demonstrate this in two replicated 3-arm trials (including a Xibrom arm). These two studies would have to also demonstrate superiority over the vehicle with InSite's dosing regimens.

Constantine J. Markos, Pharm.D., R.Ph.
Regulatory Health Project Manager

Wiley A. Chambers, M.D.
Acting Division Director

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
09/30/2010

Reference ID: 2842399

4ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA 206911	NDA Supplement N/A	If NDA, Efficacy Supplement Type: <i>(an action package is not required for SE8 or SE9 supplements)</i>
Proprietary Name: BromSite Established/Proper Name: bromfenac Dosage Form: ophthalmic solution		Applicant: InSite Vision Incorporated Agent for Applicant (if applicable): N/A
RPM:		Division:
NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		<p>For ALL 505(b)(2) applications, two months prior to EVERY action:</p> <ul style="list-style-type: none"> • Review the information in the 505(b)(2) Assessment and submit the draft² to CDER OND IO for clearance. • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) <p><input type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (notify CDER OND IO) Date of check:</p> <p><i>Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</i></p>
Actions		
<ul style="list-style-type: none"> • Proposed action • User Fee Goal Date is <u>April 10, 2016</u> 		X AP - April 8, 2016
<ul style="list-style-type: none"> • Previous actions (specify type and date for each action taken) 		X None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____		X N/A
❖ Application Characteristics ³		

¹ The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.

² For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

³ Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: Standard Priority
 Chemical classification (new NDAs only): **Type 5**
(confirm chemical classification at time of approval)

- | | |
|---|---|
| <input type="checkbox"/> Fast Track | <input type="checkbox"/> Rx-to-OTC full switch |
| <input type="checkbox"/> Rolling Review | <input type="checkbox"/> Rx-to-OTC partial switch |
| <input type="checkbox"/> Orphan drug designation | <input type="checkbox"/> Direct-to-OTC |
| <input type="checkbox"/> Breakthrough Therapy designation | |

NDAs: Subpart H

- Accelerated approval (21 CFR 314.510)
 Restricted distribution (21 CFR 314.520)

Subpart I

- Approval based on animal studies

- Submitted in response to a PMR
 Submitted in response to a PMC
 Submitted in response to a Pediatric Written Request

BLAs: Subpart E

- Accelerated approval (21 CFR 601.41)
 Restricted distribution (21 CFR 601.42)

Subpart H

- Approval based on animal studies

- REMS: MedGuide
 Communication Plan
 ETASU
 MedGuide w/o REMS
 REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 <i>(approvals only)</i>	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications <i>(approvals only)</i>	
• Office of Executive Programs (OEP) liaison has been notified of action	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Indicate what types (if any) of information were issued	<input type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
CONTENTS OF ACTION PACKAGE	
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list <i>(approvals only)</i>	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters	
❖ Copies of all action letters <i>(including approval letter with final labeling)</i>	Action and date: Approval: April 8, 2016
Labeling	
❖ Package Insert <i>(write submission/communication date at upper right of first page of PI)</i>	
• Most recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	<input type="checkbox"/> Included
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling <i>(write submission/communication date at upper right of first page of each piece)</i>	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input checked="" type="checkbox"/> None
• Most-recent draft labeling <i>(if it is division-proposed labeling, it should be in track-changes format)</i>	<input checked="" type="checkbox"/> N/A
• Original applicant-proposed labeling	<input checked="" type="checkbox"/> N/A
❖ Labels (full color carton and immediate-container labels) <i>(write submission/communication date on upper right of first page of each submission)</i>	
• Most-recent draft labeling	<input checked="" type="checkbox"/> Included
❖ Proprietary Name	Letter: 10/15/15 Review: 10/9/15
• Acceptability/non-acceptability letter(s) <i>(indicate date(s))</i>	
• Review(s) <i>(indicate date(s))</i>	
❖ Labeling reviews <i>(indicate dates of reviews)</i>	RPM: PLR Format Review: 8/11/15 DMEPA: 9/14/15 DMPP/PLT (DRISK): 3/4/16 OPDP: <input checked="" type="checkbox"/> SEALD: <input checked="" type="checkbox"/> None CSS: <input checked="" type="checkbox"/> None Product Quality <input type="checkbox"/> None Other: <input type="checkbox"/> None
Administrative / Regulatory Documents	
❖ RPM Filing Review ⁴ /Memo of Filing Meeting <i>(indicate date of each review)</i>	8/18/15
❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	3/28/16
❖ NDAs only: Exclusivity Summary <i>(signed by Division Director)</i>	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

⁴ Filing reviews for scientific disciplines are NOT required to be included in the action package.

<ul style="list-style-type: none"> • This application is on the AIP • <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No N/A N/A
❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> • Date reviewed by PeRC <u>N/A</u> If PeRC review not necessary, explain: _____ 	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, etc.) (<i>do not include previous action letters, as these are located elsewhere in package</i>)	<input checked="" type="checkbox"/> Yes
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	N/A
❖ Minutes of Meetings	
<ul style="list-style-type: none"> • If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>) 	N/A
<ul style="list-style-type: none"> • Pre-NDA/BLA meeting (<i>indicate date of mtg</i>) 	1/13/14
<ul style="list-style-type: none"> • EOP2 meeting (<i>indicate date of mtg</i>) 	2/17/12
<ul style="list-style-type: none"> • Mid-cycle Communication (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> • Late-cycle Meeting (<i>indicate date of mtg</i>) 	<input type="checkbox"/> N/A
<ul style="list-style-type: none"> • Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) (<i>indicate dates of mtgs</i>) • Other meetings 	Guidance: PIND 107723: 4/26/10
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> • Date(s) of Meeting(s) 	N/A
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Division Director Summary Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> April 8, 2016
Deputy Director Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> April 8, 2016
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> April 8, 2016
PMR/PMC Development Templates (<i>indicate total number</i>)	<input checked="" type="checkbox"/> None
Clinical	
❖ Clinical Reviews	
<ul style="list-style-type: none"> • Clinical Team Leader Review(s) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> No separate review
<ul style="list-style-type: none"> • Clinical review(s) (<i>indicate date for each review</i>) – <i>Clinical Filing Checklist and Primary Review signed by both Clinical Team Leader and Primary Clinical Reviewer</i> 	Clinical Filing Checklist: 8/12/15 Primary Review: 3/15/16
<ul style="list-style-type: none"> • Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>) 	<input checked="" type="checkbox"/> None

❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	Page 7 of 3/15/16 Clinical Review
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> N/A
❖ Risk Management <ul style="list-style-type: none"> REMS Documents and REMS Supporting Document (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ OSI Clinical Inspection Review Summary(ies) (<i>include copies of OSI letters to investigators</i>)	<input checked="" type="checkbox"/> Yes
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	N/A
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	N/A
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Statistical Review(s) (<i>indicate date for each review</i>) <i>Statistics Filing Checklist and Statistical Review and Evaluation signed by both Statistics Team Leader and Primary Statistics Reviewer</i>	Statistics Filing Checklist: 7/28/15 Statistical Review and Evaluation: 2/9/16
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> No separate review
Clinical Pharmacology review(s) (<i>indicate date for each review</i>) <i>Clinical Pharmacology Filing Checklist and Primary Clinical Pharmacology Review signed by both Clinical Pharmacology Team Leader and Primary Clinical Pharmacology Reviewer</i>	Clinical Pharmacology Filing Form: 7/27/15 Clinical Pharmacology Review: 2/9/16
❖ OSI Clinical Pharmacology Inspection Review Summary (<i>include copies of OSI letters</i>)	<input checked="" type="checkbox"/> None requested

Nonclinical <input type="checkbox"/> None	
Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
• Supervisory Review(s) (indicate date for each review)	<input checked="" type="checkbox"/> No separate review
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review) <i>Pharmacology/Toxicology Filing Checklist and Primary Pharmacology/Toxicity Review signed by both Pharmacology/Toxicology Team Leader and Primary Pharmacology/Toxicology Reviewer</i>	Pharmacology/Toxicology Filing Checklist: 7/27/15 Pharmacology/Toxicology Review: 3/15/16
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None
❖ OSI Nonclinical Inspection Review Summary (include copies of OSI letters)	<input checked="" type="checkbox"/> None requested
Product Quality <input type="checkbox"/> None	
Product Quality Discipline Reviews	
• Tertiary review (indicate date for each review)	<input type="checkbox"/> None
• Secondary review (e.g., Branch Chief) (indicate date for each review)	<input type="checkbox"/> None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) (indicate date for each review)	<input checked="" type="checkbox"/> 2/27/16
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team (indicate date of each review)	<input type="checkbox"/> None
Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	<input checked="" type="checkbox"/> 2/27/16
<input type="checkbox"/> Review & FONSI (indicate date of review)	
<input type="checkbox"/> Review & Environmental Impact Statement (indicate date of each review)	
Facilities Review/Inspection	
<input type="checkbox"/> Facilities inspections (action must be taken prior to the re-evaluation date) (only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)	<input checked="" type="checkbox"/> Acceptable Re-evaluation date: <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable

Day of Approval Activities

❖ For all 505(b)(2) applications: <ul style="list-style-type: none"> • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity) 	<input checked="" type="checkbox"/> No changes <input type="checkbox"/> New patent/exclusivity (<i>Notify CDER OND IO</i>)
<ul style="list-style-type: none"> • Finalize 505(b)(2) assessment 	<input checked="" type="checkbox"/> Done
❖ For Breakthrough Therapy (BT) Designated drugs: <ul style="list-style-type: none"> • Notify the CDER BT Program Manager 	<input checked="" type="checkbox"/> N/A
❖ For products that need to be added to the flush list (generally opioids): <u>Flush List</u> <ul style="list-style-type: none"> • Notify the Division of Online Communications, Office of Communications 	<input checked="" type="checkbox"/> N/A
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	<input checked="" type="checkbox"/> Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	N/A
❖ Ensure that proprietary name, if any, and established name are listed in the <i>Application Product Names</i> section of DARRTS, and that the proprietary name is identified as the “preferred” name	<input checked="" type="checkbox"/> Done
❖ Ensure Pediatric Record is accurate	<input checked="" type="checkbox"/> Done
❖	