

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-664**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

**PATENT INFORMATION SUBMITTED WITH THE  
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**  
*For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and  
Composition) and/or Method of Use*

NDA NUMBER

21-664

NAME OF APPLICANT / NDA HOLDER

ISTA Pharmaceuticals, Inc.

*The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.*

TRADE NAME (OR PROPOSED TRADE NAME)

XIBROM

ACTIVE INGREDIENT(S)

Bromfenac sodium hydrate

STRENGTH(S)

0.1%

DOSAGE FORM

Ophthalmic solution

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

**For hand-written or typewriter versions (only) of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

**FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.**

**For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number  
4,910,225

b. Issue Date of Patent  
20 March 1990

c. Expiration Date of Patent  
3/20/2007

d. Name of Patent Owner  
Senju Pharmaceutical Co., Ltd., Osaka Japan;  
A.H. Robins Company, Incorporated, Richmond, VA

Address (of Patent Owner)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

Wenderoth, Lin and Ponack, L.L.P.  
2033 K Street, N.W., Suite 800

City/State  
Washington D.C.

ZIP Code  
20006

FAX Number (if available)  
(202)721-8250

Telephone Number  
(202)721-8200

E-Mail Address (if available)

☞ Mr. John T. Miller

Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

- 2.1** Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No
- 2.2** Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No
- 2.3** If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No
- 2.4** Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
- 2.5** Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No
- 2.6** Does the patent claim only an intermediate?  Yes  No
- 2.7** If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

- 3.1** Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No
- 3.2** Does the patent claim only an intermediate?  Yes  No
- 3.3** If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:**

- 4.1** Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No
- 4.2** Patent Claim Number (as listed in the patent) Claim #7 Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No
- 4.2a** If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)  
Xibrom ophthalmic solution is indicated for the treatment of postoperative inflammation in patients who have undergone cataract extraction

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

**6. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

**6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)**

Date Signed



6 May 2004

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Lisa R. Grillone, Ph.D.

Address

ISTA Pharmaceuticals, Inc.  
15279 Alton Pkwy, Suite 100

City/State

Irvine, CA

ZIP Code

92618

Telephone Number

949-788-5304

FAX Number (if available)

949-7886013

E-Mail Address (if available)

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration  
CDER (HFD-007)  
5600 Fishers Lane  
Rockville, MD 20857

*An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.*

### **1.3.2 Patent Certification**

This section is not applicable because this NDA is being filed under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act.

EXCLUSIVITY SUMMARY for NDA # 21-664 SUPPL #

Trade Name XIBROM Generic Name bromfenac ophthalmic solution) 0.09%

Applicant Name ISTA Pharmaceuticals, Inc. HFD- 550  
Approval Date March 23, 2005

**PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA? YES/ X / NO / \_\_\_ /

b) Is it an effectiveness supplement? YES / \_\_\_ / NO / X /

If yes, what type (SE1, SE2, etc.)? 3S New Formulation

c) 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 / X / 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:

d) Did the applicant request exclusivity?

YES / X / NO / \_\_\_ /

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

3 years

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

YES / \_\_\_ / NO / X /

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES / \_\_\_ / NO / X /

If yes, NDA # \_\_\_\_\_ Drug Name

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

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

YES / \_\_\_ / NO / X /

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (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 # 20-535 Duract (bromfenac sodium capsules) 25mg

NDA #

NDA #

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.)

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 9. IF "YES," GO TO PART III.**

**PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S 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 9.**

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (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 9:**

- (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? *Submitted studies; did not submit a statement.*

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 /X/

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, Study # ISTA BR-CS001-ER

Investigation #2, Study # ISTA BR-CS001-WR

Investigation #3, Study #

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 YES /\_\_\_/ NO /X/

Investigation #2 YES /\_\_\_/ NO /X/

Investigation #3 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:

NDA # \_\_\_\_\_ Study #  
NDA # \_\_\_\_\_ Study #  
NDA # \_\_\_\_\_ Study #

- (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                    YES /\_\_\_/                    NO /x/  
Investigation #2                    YES /\_\_\_/                    NO /x/  
Investigation #3                    YES /\_\_\_/                    NO /\_\_\_/

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

NDA # \_\_\_\_\_ Study #  
NDA # \_\_\_\_\_ Study #  
NDA # \_\_\_\_\_ Study #

- (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, Study # ISTA BR-CS001-ER  
Investigation #2, Study # ISTA BR-CS001-WR  
Investigation #3, Study #

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 !  
IND # **60,295** YES / **x** / ! NO / \_\_\_ / Explain:  
!  
!  
!

Investigation #2 !  
IND # **60,295** 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 / \_\_\_ / Explain \_\_\_\_\_ ! NO / \_\_\_ / Explain \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

Investigation #2 !  
YES / \_\_\_ / Explain \_\_\_\_\_ ! NO / \_\_\_ / 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: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

\_\_\_\_\_  
Jennifer Harris, M.D.  
Medical Officer

\_\_\_\_\_  
Raphael Rodriguez, PM

 3/23/05  
\_\_\_\_\_  
Wiley A. Chambers, M.D.  
Deputy Director, HFD-550

cc:  
Archival NDA 21-664  
HFD-550 /Division File  
HFD-550 /RPM/ RodriguezR  
HFD-093/Mary Ann Holovac  
HFD-104/PEDS/T.Crescenzi

Form OGD-011347

### **1.3.10 Statements of Claimed Exclusivity and Associated Certifications**

#### **Statement of Claimed Marketing Exclusivity**

In accordance with 21 CFR 314.50(j), ISTA claims that XIBROM™ (bromfenac sodium ophthalmic solution) 0.1% is entitled to a 3-year period of marketing exclusivity under the provisions of 21 CFR 314.80(b)(4). This product meets the criteria outlined in that section of the regulations as follows:

- (i) Is being submitted under section 505(b) of the act.
- (ii) Will be approved after September 24, 1984.
- (iii) Is for a drug product that contains an active moiety that has been previously approved in another application under section 505(b) of the act, specifically NDA 20-535 for Duract®, a formulation of bromfenac sodium for oral administration, held by Wyeth Pharmaceuticals, Inc.
- (iv) Contains reports of new clinical investigations (other than bioavailability studies) conducted and sponsored by ISTA that are essential to approval of the application, specifically phase III studies ISTA-BR-CS001 - ER and ISTA-BR-CS001 - WR.



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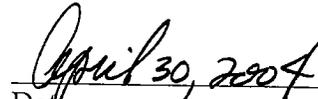
[www.istavision.com](http://www.istavision.com)

**Debarment Certification for NDA 21-664 for  
XIBROM 0.1% (bromfenac sodium ophthalmic solution)**

ISTA Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Signed:

  
Marvin J. Garrett  
Vice President  
Regulatory Affairs, Quality & Compliance

  
Date

## PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

DA/BLA #: 21-664 Supplement Type (e.g. SE5): \_\_\_\_\_ Supplement Number: \_\_\_\_\_

Stamp Date: May 28, 2004 Action Date: March 22, 2005

HFD 550 Trade and generic names/dosage form: XIBROM (bromfenac ophthalmic solution)0.09%

Applicant: ISTA pharmaceutical, Inc. Therapeutic Class: nonsteroid anti-inflammatory

Indication(s) previously approved: None

**Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.**

Number of indications for this application(s): 1

Indication #1: Indicated for the treatment of postoperative inflammation in patients who have undergone cataract extraction.

Is there a full waiver for this indication (check one)?

**XX** Yes: Please proceed to Section A.

No: Please check all that apply: \_\_\_ Partial Waiver \_\_\_ Deferred \_\_\_ Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

### Section A: Fully Waived Studies

Reason(s) for full waiver:

*The applicant requested a waiver of pediatric studies on the basis that this drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients (age 16 years and under) and is not likely to be used in a substantial number of pediatric patients.*

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: \_\_\_\_\_

*If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.*

### Section B: Partially Waived Studies

Age range being partially waived:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study

- There are safety concerns
- Adult studies ready for approval
- Formulation needed

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
 Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
 Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

\_\_\_\_\_  
Jennifer Harris, M.D., Medical Officer

 3/23/05  
 \_\_\_\_\_  
 Wiley A. Chambers, M.D.  
 Deputy Director, HFD-550

cc: NDA 21-664  
 HFD-950/ Terrie Crescenzi  
 HFD-960/ Grace Carmouze  
 (revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960  
 301-594-7337

### **1.3.8 Waiver Requests**

#### **Waiver for Pediatric Studies**

ISTA requested a waiver of pediatric studies on the basis that this drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients (age 16 years and younger) and is not likely to be used in a substantial number of pediatric patients [21CFR 314.55(c)(2)(i) and 21 CFR 201.57(a)(9)]. The request was submitted to IND 60, 296 in Amendment 034 (February 24, 2004). In their response to ISTA prior to the Pre-NDA teleconference on April 9, 2004 (Item 6 in attached document) and in a communication dated April 13, 2004 (attached e-mail), FDA indicated that they agreed with this waiver request.

3 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

Withheld Track Number: Administrative-1

 STA  
Pharmaceuticals

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NDA 21-664  
Amendment 14 to Original Application

March 17, 2005

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anti-Inflammatory, Analgesic & Ophthalmic Drug  
Products (HFD-550)  
Document Control Room (N115)  
9201 Corporate Blvd., Corp. 2  
Rockville, MD 20850

Re: **NDA 21-664: XIBROM™ (bromfenac ophthalmic solution) 0.09%**  
**Amendment 14: Updated draft package insert labeling for Xibrom drug product**

Dear Reviewers:

Pursuant to 21CFR 314.60, ISTA Pharmaceuticals, Inc. (ISTA) submits herein Amendment 14 to XIBROM™ (bromfenac ophthalmic solution) 0.09% original application (NDA 21-664, submitted 05-24-04). Reference is made to previous Xibrom draft labeling submissions dated February 22, 2005 (Amendment 7) and March 15, 2005 (Amendment 13). Reference is made also to the electronic communications dated March 15 and 17, 2005 in which the Agency provided ISTA the recommended Xibrom drug product labeling. Further reference is made to the telephone conference held on March 17, 2005 between representatives from the Agency and ISTA.

ISTA submits in this Amendment 14 the Xibrom drug product labeling updated per the recent Agency's Xibrom labeling recommendation (Raphael Rodriguez e-mail on 03-17-05) and comments via teleconference call on March 17, 2005. Also incorporated in this draft labeling are the editorial format changes recommended by Raphael on 03-17-05. The draft labeling is presented with annotations in red.

If you have any questions, please do not hesitate to contact me at (949) 788-5303 or via email at [mgarrett@istavision.com](mailto:mgarrett@istavision.com).

Sincerely,  
ISTA Pharmaceuticals, Inc.



Marvin J. Garrett  
Vice President  
Regulatory Affairs, Quality & Compliance

cc: Raphael Rodriguez, Regulatory Project Manager



March 15, 2005

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Wiley Chambers, M.D.  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anti-Inflammatory, Analgesic  
& Ophthalmic Drug Products (HFD-550)  
Document Control Room (N115)  
9201 Corporate Blvd., Corp 2  
Rockville, MD 20850

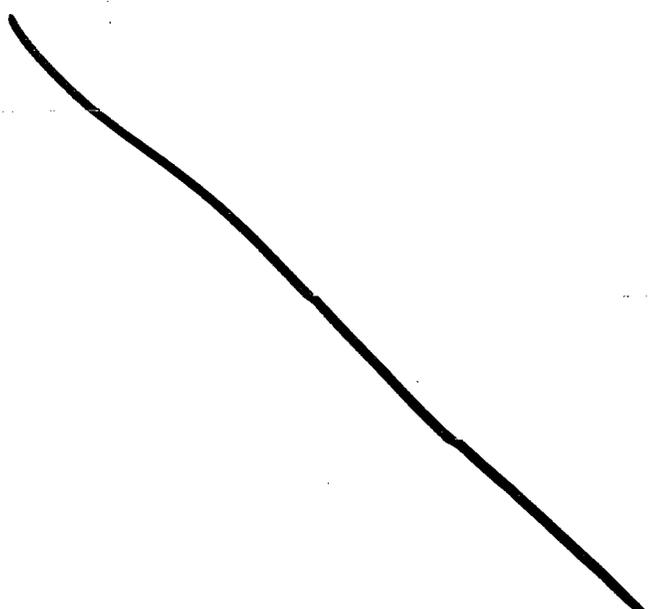
**Re: NDA 21-664 XIBROM™ (bromfenac sodium ophthalmic solution)  
0.1035%; Amendment 13 – Draft Package Insert Label Revision**

Dear Dr. Chambers:

[www.istavision.com](http://www.istavision.com)

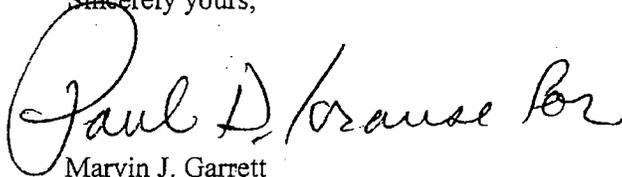
We acknowledge receipt of an email from Raphael Rodriguez on March 15, 2005 which contained the proposed XIBROM package insert from the Agency and requested our acceptance or comments.

In Amendment 13, we have submitted a proposed annotated revision of the Agency's proposed package insert. The justifications listed below follow the annotated numbering on the submitted package insert:



If you have any questions regarding this submission, please feel free to contact me at (949) 788-5303 or via email at [mgarrett@istavision.com](mailto:mgarrett@istavision.com).

Sincerely yours,

A handwritten signature in cursive script that reads "Paul D. Krause for". The signature is written in black ink and is positioned above the typed name and title.

Marvin J. Garrett  
Vice President, Regulatory Affairs, Quality and Compliance  
ISTA Pharmaceuticals, Inc.

ORIGINAL

Pharmaceuticals

NDA 21-664  
Amendment 12 to Original Application

RECEIVED

MAR 11 2005

MEGA / CDER

295 Alton Parkway

March 10, 2005

Irvine, CA 92618

Wiley Chambers, MD  
Food and Drug Administration  
Division of Anti-Inflammatory, Analgesic  
& Ophthalmic Drug Products (HFD-550)  
Document Control Room (N115)  
9201 Corporate Blvd., Corp 2  
Rockville, MD 20850

949) 788-6000

fax 949) 788-6010

N 000(L)  
NEW CORRESP

**Re: NDA 21-664 XIBROM™ (bromfenac sodium ophthalmic solution)  
0.1035%  
Amendment 12: Updated Manufacturing Batch Record to Reflect the  
Label Change to 0.1035%**

[www.istavision.com](http://www.istavision.com)

Dear Dr. Chambers:

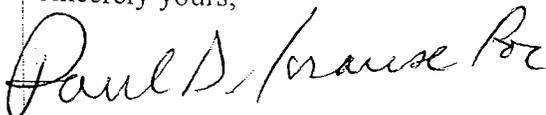
Pursuant to 21CFR 314.60, ISTA Pharmaceuticals, Inc. (ISTA) submits herein an archival and review copies of Amendment 12 to XIBROM (bromfenac sodium ophthalmic solution) 0.1035% original application (NDA 21-664, submitted 05-24-04).

Amendment 12 contains the requested marked-up copy of the Compounding Bill of Materials for Xibrom which reflects the changes that will be made to the manufacturing documentation for Xibrom following the label change to 0.1035% for the API.

ISTA Pharmaceuticals, Inc. certifies that a true copy of this Amendment 12 was provided to the Los Angeles District office on the same submission date to the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products in accordance with 21CFR 314.60, (c).

Should you require additional information or have any questions/comments regarding this submission, please feel free to contact me at (949) 788-5303 or via email at [mgarrett@istavision.com](mailto:mgarrett@istavision.com).

Sincerely yours,



Marvin J. Garrett  
Vice President, Regulatory Affairs, Quality Assurance and Compliance  
ISTA Pharmaceuticals, Inc.

DUPLICATE

Pharmaceuticals

NDA 21-664  
Amendment 09 to Original Application

5 Alton Parkway

Irvine, CA 92618

949) 788-6000

fax 949) 788-6010

March 4, 2005

Wiley Chambers, MD  
Food and Drug Administration  
Division of Anti-Inflammatory, Analgesic  
& Ophthalmic Drug Products (HFD-550)  
Document Control Room (N115)  
9201 Corporate Blvd., Corp 2  
Rockville, MD 20850

RECEIVED  
MAR 07 2005  
MEGA / CDER

N-000 (BC)  
ORIG AMENDMENT

www.istavision.com

**Re: NA 21-664 XIBROM (bromfenac sodium ophthalmic solution) 0.1%  
Amendment 09: Updated Drug Product Specifications -Sodium Sulfite  
Shelf-life Specification**

Dear Dr. Chambers:

Pursuant to 21CFR 314.60, ISTA Pharmaceuticals, Inc. (ISTA) submits herein Amendment 09, in duplicate to XIBROM (bromfenac sodium ophthalmic solution) 0.1% original application (NDA 21-664, submitted 05-24-04).

ISTA is responding to an e-mail (**Attachment 1**) received from Dr. Yong De Lu dated March 3, 2005. As noted in the e-mail, Dr. Lu recommended the shelf-life specification for sodium sulfite be NLT [redacted] of theoretical formulated amount. ISTA accepts the specification of NLT [redacted] for sodium sulfite content as a shelf-life specification. ISTA will continue to monitor the sodium sulfite in the stability programs established and will notify the Agency should the established shelf-life specification of NLT [redacted] requires adjustment.

A revised **Table 1: Drug Product Specification (Attachment 2)** is included in this amendment wherein the sodium sulfite shelf-life specification is revised to NLT [redacted]

ISTA believes the stability data previously submitted support a [redacted] expiry date.

ISTA Pharmaceuticals, Inc. certifies that a true copy of this Amendment 9 was provided to the Los Angeles District office on the same submission date to the Division of Anti-Inflammatory, Analgesic, and Ophthalmic Drug Products in accordance with 21CFR 314.60, (c).

ORIGINAL

Pharmaceuticals

NDA 21-664  
Amendment 07 to Original Application

5 Alton Parkway

Irvine, CA 92618

949) 788-6000

fax 949) 788-6010

February 22, 2005

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anti-Inflammatory, Analgesic & Ophthalmic Drug  
Products (HFD-550)  
Document Control Room (N115)  
9201 Corporate Blvd., Corp. 2  
Rockville, MD 20850

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FEB 24 2005

MEGA / CDER

ORIG AMENDMENT

N-000(BL)

**Re: NDA 21-664: XIBROM™ (bromfenac sodium ophthalmic solution) 0.1%  
Amendment 07: Updated draft labeling for drug product package insert,  
container and carton**

Dear Reviewers:

[www.istavision.com](http://www.istavision.com)

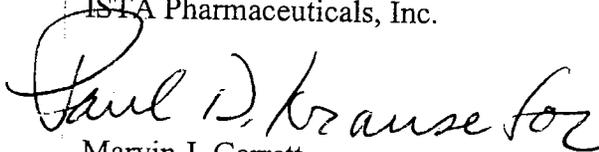
Pursuant to 21CFR 314.60, ISTA Pharmaceuticals, Inc. (ISTA) submits herein Amendment 07 to XIBROM™ (bromfenac sodium ophthalmic solution) 0.1% original application (NDA 21-664, submitted 05-24-04). This submission contains the proposed changes to XIBROM™ (bromfenac sodium ophthalmic solution) 0.1% :

1. Package Insert
2. Container and Carton Labels (2.5 mL and 5 mL)

A summary of the proposed changes to the labeling is provided following this page. Included also in this submission is the mock labeling for the above items.

If you have any questions, please do not hesitate to contact me at (949) 788-5303 or via email at [mgarrett@istavision.com](mailto:mgarrett@istavision.com).

Sincerely,  
ISTA Pharmaceuticals, Inc.



Marvin J. Garrett  
Vice President  
Regulatory Affairs, Quality & Compliance

cc: Raphael Rodriguez, Regulatory Project Manager

February 11, 2005

**NDA 21-664**

**XIBROM™ (bromfenac sodium ophthalmic solution) 0.1%**

**CMC COMMENTS**

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issue under consideration. Otherwise, provide the appropriate information as an amendment to the submission.

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The decrease of sodium sulfite concentration to zero is not acceptable during the storage of the drug product, an acceptance criterion of NLT **—** for the sodium sulfite in the shelf-life specification should be proposed.

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this page is the manifestation of the electronic signature.**  
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/s/

-----  
Yong-De Lu  
2/11/05 04:44:20 PM  
CHEMIST

February 9, 2005

**NDA 21-664**

**XIBROM™ (bromfenac sodium ophthalmic solution) 0.1%**

**CMC COMMENTS**

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issue under consideration. Otherwise, provide the appropriate information as an amendment to the submission.

1. Based on the available stability data for the drug product, please revised the acceptance criterion for BAK assay to
2. For assay of sodium sulfite, please propose an acceptance range in the drug product specification.
3. If USP methods are cited for the Sterility and Antimicrobial Effectiveness Test, the corresponding USP references should be listed in the specification.
4. Submit the revised specification for the drug product.
5. Update the stability data for the Xibrom Ophthalmic Solution, 0.1% drug product.

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/s/

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Yong-De Lu  
2/11/05 04:37:03 PM  
CHEMIST

Pharmaceuticals

RECEIVED

FEB 04 2005

MEGA / CDER

February 2, 2005

N-000(C)

NEW CORRESP

555 Alton Parkway

Rockville, CA 92618

Phone: 949-788-6000

Fax: 949-788-6010

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anti-Inflammatory, Analgesic & Ophthalmic Drug  
Products (HFD-550)  
Document Control Room (N115)  
9201 Corporate Blvd., Corp. 2  
Rockville, MD 20850

**Re: NDA 21-664: XIBROM™ (bromfenac sodium ophthalmic solution) 0.1%  
Amendment 06: Additional Safety Update Reports following the 120-Day  
Safety Update**

Dear Reviewers:

[www.istavision.com](http://www.istavision.com)

Under the provisions of 21 CFR 314.50(d)(5)(vi)(b), we are submitting additional safety update reports following the 120-day safety update to the original NDA for Xibrom, which was submitted on May 24, 2004. ISTA has not conducted any clinical studies with bromfenac sodium ophthalmic solution 0.1% since the Phase III studies that were fully reported in the NDA. In addition, there have been no subsequent literature reports that address the safety of bromfenac.

With respect to postmarketing experience in Japan, the original NDA included all Periodic Safety Update Reports (PSURs) available from Senju Pharmaceutical Co., Ltd. A list of adverse events in Japan that have been reported to Senju since the submission of the 120-day safety update is enclosed. These adverse events do not change the safety conclusions as they were reported in the original NDA and do not require any change in the proposed labeling for Xibrom.

If you have any questions, please do not hesitate to contact me at (949) 788-5303 or via email at [mgarrett@istavision.com](mailto:mgarrett@istavision.com).

Sincerely,  
ISTA Pharmaceuticals, Inc.



Marvin J. Garrett  
Vice President  
Regulatory Affairs, Quality & Compliance

ORIGINAL

cc: Raphael Rodriguez, Regulatory Project Manager

January 26, 2005

NDA 21-664

XIBROM™ (bromfenac sodium ophthalmic solution) 0.1%

CMC COMMENTS

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If your response can be found in the contents of your submission, just cite those sections of the submission that are relevant to the issue under consideration. Otherwise, provide the appropriate information as an amendment to the submission.



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/s/

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Yong-De Lu  
2/11/05 04:48:31 PM  
CHEMIST

ISTA Pharmaceuticals

NDA 21-664  
Amendment 04 to Original Application

November 3, 2004

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anti-Inflammatory, Analgesic  
& Ophthalmic Drug Products (HFD-550)  
Document Control Room (N115)  
9201 Corporate Blvd., Building 2  
Rockville, MD 20850

Re: **NDA 21-664 XIBROM (bromfenac sodium ophthalmic solution) 0.1%**  
**Amendment 04: Responses to FDA Microbiology Comments**

Dear Reviewers:

Pursuant to 21CFR 314.60, ISTA Pharmaceuticals, Inc. (ISTA) submits herein Amendment 04 to XIBROM (bromfenac sodium ophthalmic solution) 0.1% original application (NDA 21-664, submitted 05-24-04). ISTA's responses to the FDA Microbiology comments are presented in the same order the comments are written in the Agency's electronic mail received on October 21, 2004 from Raphael Rodriguez. A copy of this e-mail is provided as Attachment 1.

Should you require additional information or have any questions/comments regarding this submission, please feel free to contact me at (949) 788-5303 or via email at [mgarrett@istavision.com](mailto:mgarrett@istavision.com).

Sincerely yours,



Marvin J. Garrett  
Vice President, Regulatory Affairs, Quality and Compliance  
ISTA Pharmaceuticals, Inc.

cc: Raphael Rodriguez, Project Manager

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NOV 05 2004  
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N-000(BI)

ORIG AMENDMENT

ORIGINAL

1 Page(s) Withheld

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Draft Labeling

Deliberative Process



Pharmaceuticals

NDA 21-664

August 13, 2004

15279 Alton Parkway, Suite 100

Irvine, CA 92618

949) 788-6000

fax 949) 788-6010

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anti-Inflammatory, Analgesic  
& Ophthalmic Drug Products  
Document Control Room (N115)  
9201 Corporate Blvd, Building 2  
Rockville, MD 20850

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AUG 16 2004  
MEGA/CDER

Re: NDA 21-664 Xibrom (bromfenac sodium ophthalmic solution) 0.1%  
Amendment #02: Clinical Information Request

N-000(BM)  
ORIG AMENDMENT

Dear Reviewers:

Reference is made to a forwarded email sent to ISTA containing this message:

www.istavision.com

**"The per-protocol population as defined in the study report is not a "true" per-protocol population (i.e., no protocol violations). Please conduct the efficacy analysis for the "true" per-protocol population observed cases only for both of the phase 3 studies submitted in the NDA."**

The methods to be used to define the protocol-compliant ("per protocol") subject population were provided in the amended Statistical Analysis Plan submitted to the Agency on January 23, 2004 (IND 60,295, Amendment #029, Protocol is dated January 21, 2004). We interpret the statement above as a request for a *different* definition of "per-protocol", and that the reviewer is requesting a redefinition of the per-protocol population, in which all subjects with protocol-violation forms (i.e., observed cases) would be excluded from the efficacy analysis.

In the context of an alternate proposal, it is important to note that a proportion of the protocol-violation forms document administrative errors that do not affect the efficacy endpoint. For example, errors in procedure by study site personnel (e.g., "study staff did not assess uncorrected visual acuity with pinhole") or use of rescue medications administered *after* efficacy assessment would have no impact on the primary endpoint outcome. Further, exclusion of subjects of this type from a per-protocol analysis would result in sample sizes too small to draw conclusions about the relative effectiveness of bromfenac versus placebo. Thus, we did not exclude subjects with 'administrative violations' in the per-protocol analysis provided as a response to the clinical reviewer's question.

The new analysis does exclude subjects with one or more major (i.e., non-administrative) protocol violation and subjects who received rescue medications before assessment of the primary efficacy endpoint. The analysis thus excludes the following categories of subject: Those with eligibility violations, those with missing study visits or out-of-window visits, those with Test Agent administration errors of any type, and those who received disallowed medications before Visit 4 (Day 15, at which efficacy was assessed). Detailed methods are included as Attachment 1.

DUPLICATE

**Results:**

The results of the analysis are shown in Attachment 2, and are summarized below:

		n	Bromfenac	Placebo	p-value
ER	ITT	296	124/198 (62.6%)	39/98 (39.8%)	0.0002
	PP1*	150	74/117 (63.2%)	12/33 (36.4%)	0.0058
	PP2†	127	53/84 (63.1%)	19/43 (44.2%)	0.0418
WR	ITT	231	104/158 (65.8%)	35/73 (47.9%)	0.0099
	PP1*	123	65/90 (72.2%)	18/33 (54.5%)	0.0637
	PP2†	120	50/76 (65.8%)	22/44 (50.0%)	0.0889

\*Original per-protocol (protocol-compliant) population submitted in the NDA

†New per-protocol population

Listings of all subjects with protocol violation forms are attached for the reviewers' convenience as Attachment 3. Tables 5.1 and 5.2 in Attachment 3 list two categories of subjects with protocol violations from study ER (Eastern Region): subjects listed in Table 5.1 are those with non-administrative protocol violations excluded from the revised per-protocol analysis, while subjects in Table 5.2 are those with only administrative violations who were included in the analysis. Tables 5.3 and 5.4 in Attachment 3 provide the same information for study WR (Western Region).

**Discussion:**

Redefinition of the per-protocol population produces results which are substantially the same as those presented in the original per-protocol population: in both studies, the inflammation clearance rate is higher in the bromfenac group than in the placebo group. As reported in the final study reports, the difference between the treatment groups in the original per-protocol population is statistically significant in the Eastern Region ( $p=0.0058$ ) and not significant in the Western Region ( $p=0.0637$ ). In the new analysis, differences are similarly significant for the East ( $p=0.0418$ ) and not significant for the West ( $p=0.0889$ ). Since differences in clearance rates between the treatment groups are consistent in all analyses, the increase in p-values for the per-protocol analyses versus the intent-to-treat analyses (the primary efficacy outcome on both studies) are clearly due to the decrease in sample size when some subjects are excluded from the study populations. Clearance rates seen in both the original per-protocol analysis and the new analysis are consistent with results reported for bromfenac trials in Japan.

**Conclusions:**

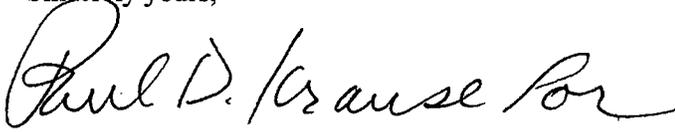
Exclusion of subjects with protocol violations (observed cases) does not change the efficacy results in either study from those presented in the NDA submission. While the power to detect a statistically significant difference between treatment groups is less in all per-protocol analyses due to decreased subject numbers, the essential conclusion reached in the intent-to-treat analyses is supported by the per-protocol results, that bromfenac is effective in the treatment of post cataract surgery inflammation.

If you have any questions regarding this submission, please feel free to contact me at (949)788-5303 or vial email at [mgarrett@istavision.com](mailto:mgarrett@istavision.com).

XIBROM™ (bromfenac sodium ophthalmic solution) 0.1%  
NDA 21-664

ISTA Pharmaceuticals, Inc.

Sincerely yours,

A handwritten signature in cursive script that reads "Paul D. Krause for". The signature is written in black ink and is positioned above the typed name and title.

Marvin J. Garrett  
Vice President, Regulatory Affairs, Quality and Compliance

Cc: Raphael Rodriguez, Regulatory Project Manager



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-664

ISTA Pharmaceuticals, Inc.  
Attention: Marvin Garrett  
Vice President, Regulatory Affairs  
Quality & Compliance  
15279 Alton Parkway, Suite 100  
Irvine, CA 92618

Dear Mr. Garrett:

Please refer to your May 24, 2004, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Xibrom (brofenac sodium ophthalmic solution) 0.1%.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application was filed under section 505(b) of the Act on July 23, 2004, in accordance with 21 CFR 314.101(a).

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

If you have any questions, call Raphael R. Rodriguez, Regulatory Project Manager, at (301) 827-2090.

Sincerely,

*{See appended electronic signature page}*

Carmen DeBellas, R.Ph.  
Chief, Project Management Staff  
Division of Anti-Inflammatory, Analgesic,  
and Ophthalmic Drug Products, HFD-550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

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/s/

-----  
Carmen DeBellas  
7/29/04 02:16:44 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 21-664

ISTA Pharmaceuticals, Inc.  
Attention: Marvin Garrett  
Vice President, Regulatory Affairs  
Quality & Compliance  
15279 Alton Parkway, Suite 100  
Irvine, CA 92618

Dear Mr. Garrett:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Xibrom (brofenac sodium ophthalmic solution)0.1%

Review Priority Classification: Standard (S)

Date of Application: May 24, 2004

Date of Receipt: May 28, 2004

Our Reference Number: NDA 21-664

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 July 23, 2004, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be March 26, 2005.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application. Once the application has been filed we will notify you whether we have waived the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:

Center for Drug Evaluation and Research  
Division of Anti-Inflammatory, Analgesic and  
Ophthalmic Drug Products, HFD-550  
Attention: Division Document Room  
5901-B Ammendale Road  
Beltsville, MD 20705

Courier/Overnight Mail:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anti-Inflammatory, Analgesic and  
Ophthalmic Drug Products, HFD-550  
Attention: Division Document Room  
9201 Corporate Blvd.  
Rockville, MD 20850

If you have any questions, call Raphael R. Rodriguez, Regulatory Project Manager, at (301) 827-2090.

Sincerely,

*{See appended electronic signature page}*

Carmen DeBellas, R. Ph.  
Chief, Project Management  
Division of Anti-Inflammatory, Analgesic,  
and Ophthalmic Drug Products, HFD-550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

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/s/

-----  
Raphael Rodriguez  
7/14/04 08:02:08 AM



July 7, 2004

15279 Alton Parkway, Suite 100

Irvine, CA 92618

949 788-6000

fax 949 788-6010

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Anti-Inflammatory, Analgesic  
& Ophthalmic Drug Products (HFD-550)  
Document Control Room (N115)  
9201 Corporate Blvd., Building 2  
Rockville, MD 20850

**Re: NDA 21-664 XIBROM (bromfenac sodium ophthalmic solution) 0.1%  
Amendment #1: Request for Waiver of Evidence of In Vivo Bioavailability**

Dear Reviewers:

[www.fda.gov/cder/rdmt](http://www.fda.gov/cder/rdmt)

Reference is made to 21CFR 320.22(e) which allows FDA, for good cause, to grant a waiver for submission of evidence of bioavailability if the waiver is compatible with protection of public health.

Under NDA 21-664 section 5.3.3.1, (found in Module 5, volume 1) ISTA submitted Study G-01 entitled "Phase 1 clinical study of bromfenac sodium ophthalmic solution four week safety study of bromfenac ophthalmic solution (0.1% and 0.2%) in Japanese health volunteers". Part of this phase 1 evaluation was an assessment of blood levels of bromfenac. The analytical method for this study is found in section 5.3.1.4. This method was not validated nor was an analytical report provided for this pharmacokinetic study.

It is unlikely that conducting a retrospective analytical method validation or conducting an entirely new study will create any meaningful information. Study G-01 used an HPLC analytical method with a detection limit of \_\_\_\_\_ for bromfenac sodium. A single dose 50  $\mu$ L drop of 0.1% solution contains \_\_\_\_\_ of drug. If one assumes 100% absorption (highly unlikely assumption), then the blood concentration (assuming 2500 mL human blood volume) would approximate \_\_\_\_\_. To conduct a pharmacokinetic study in humans that generates useful information, one would likely need an analytical method with a detection limit of \_\_\_\_\_. This detection level is unlikely to be achieved.

The forgoing should be contrasted with the data presented in Study F-27 entitled "Metabolic disposition of  $^{14}$ C-bromfenac in healthy volunteers after a single [oral] dose 50 mg dose of  $^{14}$ C-bromfenac, as the sodium salt" found in section 5.3.3.1, volume 2. This study is also known as Wyeth-Ayerst Report GTR 21-847 which was submitted in support of Wyeth-Ayerst NDA 20-535. This study is a rather



definitive study of the disposition of bromfenac sodium following oral administration.

15279 Alton Parkway, Suite 100

Irvine, CA 92618

949 788-6000

fax 949 788-6010

It is well known that topical administration of 50  $\mu\text{L}$  drops of drug solutions to the eye results in a significant portion that drains down the lacrimal duct to the throat where it is swallowed and transported to the stomach and intestines for absorption. The current thinking is that something close to 40  $\mu\text{L}$  of a 50  $\mu\text{L}$  drop is washed by natural tear flow down the lacrimal duct within a short period of time. This is a technological limit of conventional ophthalmic dosing. Therefore, a 50  $\mu\text{L}$  drop is largely an oral dose of drug product.

In summary, because of analytical method limitations and dosing limitations there is little possibility that useful pharmacokinetic data can be generated on ophthalmic administration of a 0.1% solution, whether the submitted study method (G-01) is validated or even if an entirely new study were performed. Since a topical ophthalmic dose is largely an oral dose, and since a definitive oral dosage study is in the submission (Study F-27), it is unlikely that additional useful pharmacokinetic data or safety information will be generated.

[www.istavision.com](http://www.istavision.com)

In light of the above, when the low incidence of side effects and the power of the statistics supporting the anti-inflammatory and pain claims in this NDA are taken into account, it is reasonable to conclude granting a waiver for in vivo bioavailability is compatible with the protection of public health.

If you have any questions regarding this submission, please feel free to contact me at (949) 788-5303 or via email at [mgarrett@istavision.com](mailto:mgarrett@istavision.com).

Sincerely yours,

A handwritten signature in cursive script that reads "Paul D. Krause for".

Marvin J. Garrett  
Vice President, Regulatory Affairs, Quality and Compliance  
ISTA Pharmaceuticals, Inc.

cc: Raphael Rodriguez, Project Manager



15279 Alton Parkway, Suite 100

Irvine, CA 92618

949) 788-6000

fax 949) 788-6010

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May 24, 2004

Central Document Room  
Center for Drug Evaluation and Research  
Food and Drug Administration  
12229 Wilkins Avenue  
Rockville, MD 20852-1833

**Re: NDA 21-664, Original NDA for  
XIBROM™ (bromfenac sodium ophthalmic solution) 0.1%**

Dear Reviewers:

In accordance with 505(b)(1) of the Food, Drug and Cosmetic Act and 21 CFR 314.50, ISTA Pharmaceuticals, Inc. (ISTA) submits this original New Drug Application (NDA) for XIBROM™ (bromfenac sodium ophthalmic solution) 0.1%. The proposed indication for XIBROM is for the treatment of postoperative inflammation in patients who have undergone cataract extraction.

Bromfenac was originally developed as an ophthalmic solution by Senju Pharmaceuticals Co., Ltd, who licensed this product to ISTA. Phase III development in the U.S. has been conducted under IND 60,295. This submission is provided in CTD format, as agreed upon between the Division of Anti-Inflammatory, Analgesic & Ophthalmic Drug Products and ISTA at the August 12, 2003 pre-NDA teleconference and in subsequent interactions. Also as agreed upon with the Division, 18 copies are provided of Modules 1 and 2.

This submission is provided in paper except for one CD-ROM with electronic submission of the SAS XPORT transport files and the draft labeling (in Word and PDF). A separate cover letter is provided for that CD-ROM. Although that letter (which is included electronically on the CD-ROM) indicates that the size of the electronic files is approximately 113 MB, the final version of the files on the CD-ROM is actually about 250 MB.

The user fee check to the FDA for this application was sent to the Mellon Client Service Center on May 19, 2004 under the User Fee Identification Number 4776.

NDA 21-664: XIBROM™ (bromfenac sodium ophthalmic solution) 0.1%  
ISTA Pharmaceuticals, Inc.

---

The contact person for all correspondence concerning this NDA is:

Marvin J. Garrett  
V.P. Regulatory Affairs, Quality & Compliance  
Telephone: (949) 788-5303  
E-mail: [mgarrett@istavision.com](mailto:mgarrett@istavision.com)  
Fax: 949-727-0833

We look forward to your review of this NDA. If you have any questions or comments, please do not hesitate to contact me.

Sincerely,  
ISTA Pharmaceuticals, Inc.



Marvin J. Garrett  
V.P. Regulatory Affairs, Quality & Compliance

cc (cover letter): Raphael Rodriguez, Project Manager

May 24, 2004

15279 Alton Parkway, Suite 100

Irvine, CA 92618

949) 788-6000

fax 949) 788-6010

Central Document Room  
Center for Drug Evaluation and Research  
Food and Drug Administration  
12229 Wilkins Avenue  
Rockville, MD 20852-1833

**Re: NDA 21-664, Original NDA for  
XIBROM™ (bromfenac sodium ophthalmic solution) 0.1%  
SAS XPORT Transport Files**

[www.istavision.com](http://www.istavision.com)

Dear Reviewers:

Enclosed as part of the original New Drug Application (NDA) for XIBROM™ (bromfenac sodium ophthalmic solution) 0.1% is one compact disk (CD) containing SAS XPORT transport files for the two U.S. Phase 3 clinical trials and draft labeling, in both Word and pdf format. This is the only electronic portion of this NDA.

The media provided for these files is one CD-ROM with a size of approximately 113 MB. The electronic files were checked using Norton AntiVirus version 5.00.01a (Symantec) and were determined to be virus-free.

The contact person for all correspondence concerning this NDA is:

Marvin J. Garrett  
V.P. Regulatory Affairs, Quality & Compliance  
Telephone: (949) 788-5303  
E-mail: [mgarrett@istavision.com](mailto:mgarrett@istavision.com)  
Fax: 949-727-0833

If you have any questions or comments, please do not hesitate to contact me.

Sincerely,  
ISTA Pharmaceuticals, Inc.



Marvin J. Garrett  
V.P. Regulatory Affairs, Quality & Compliance

cc (cover letter): Raphael Rodriguez, Project Manager

**CONSULTATION RESPONSE**

**DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT  
OFFICE OF DRUG SAFETY  
(DMETS; HFD-420)**

<b>DATE RECEIVED:</b> 3/12/04	<b>DESIRED COMPLETION DATE:</b> 5/11/04 <b>PDUFA DATE:</b> 3/26/05	<b>ODS CONSULT #:</b> 04-0101
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**TO:** Brian Harvey, MD, PhD  
Acting Director, Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products  
HFD-550

**THROUGH:** Raphael Rodriguez  
Project Manager  
HFD-550

**PRODUCT NAME:**  
**Xibrom™**  
(Bromfenac Sodium Ophthalmic Solution)  
0.1%

**NDA SPONSOR:** ISTA Pharmaceuticals, Inc.

**NDA#:** 21-664

**SAFETY EVALUATOR:** Felicia Duffy, RN

**RECOMMENDATIONS:**

1. DMETS has no objections to the use of the proprietary name, Xibrom. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated upon submission of the NDA and approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.
2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review in order to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary name Xibrom acceptable from a promotional perspective.

Carol Holquist, RPh  
Director  
Division of Medication Errors and Technical Support  
Office of Drug Safety  
Phone: (301) 827-3242      Fax: (301) 443-9664

**Division of Medication Errors and Technical Support (DMETS)  
Office of Drug Safety  
HFD-420; PKLN Rm. 6-34  
Center for Drug Evaluation and Research**

**PROPRIETARY NAME REVIEW**

**DATE OF REVIEW:** May 14, 2004

**NDA #** 21-664

**NAME OF DRUG:** Xibrom™  
(Bromfenac Sodium Ophthalmic Solution)  
0.1%

**IND HOLDER:** ISTA Pharmaceuticals, Inc.

**\*\*\*NOTE:** This review contains proprietary and confidential information that should not be released to the public.\*\*\*

**I. INTRODUCTION:**

This consult was written in response to a request from the Division of Anti-Inflammatory, Analgesic, and Ophthalmologic Drug Products (HFD-550), for assessment of the proprietary name, "Xibrom", regarding potential name confusion with other proprietary or established drug names. Draft container labels, and carton labeling were provided for review and comment.

**PRODUCT INFORMATION**

Xibrom (Bromfenac Sodium) is an ophthalmic solution indicated for the treatment of postoperative inflammation in patients who have undergone cataract extraction. Xibrom will be available in a strength of 0.1% in 2.5 mL and 5 mL sterile bottles. The usual adult dose will be one drop in the affected eye(s) twice daily beginning 24 hours after cataract surgery and continuing through the first two weeks of the postoperative period.

**II. RISK ASSESSMENT:**

The medication error staff of DMETS conducted a search of several standard published drug product reference texts<sup>1,2</sup>, as well as several FDA databases<sup>3</sup> for existing drug names which sound-alike or look-alike to Xibrom to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted<sup>4</sup>. The Saegis<sup>5</sup> Pharma-In-Use

<sup>1</sup> MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.

<sup>2</sup> Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

<sup>3</sup> AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.

<sup>4</sup> WWW location <http://www.uspto.gov/tmdb/index.html>.

database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Xibrom. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Xibrom acceptable from a promotional perspective.
2. The Expert Panel identified three proprietary names that were thought to have the potential for confusion with Xibrom. Upon independent analysis, one additional name was identified to have the potential for confusion with Xibrom. These products are listed in table 1 (see pages 3 and 4), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Xibrom	Bromfenac Sodium Ophthalmic Solution: 0.1%	One drop in the affected eye(s) twice daily for 2 weeks.	
Librium	Chlordiazepoxide HCl Capsules: 5 mg, 10 mg, and 25 mg Powder for Injection: 100 mg/amp	<u>Mild-moderate anxiety:</u> 5 mg or 10 mg by mouth three to four times daily.  <u>Severe anxiety:</u> 20 mg or 25 mg by mouth three to four times daily. OR 50 mg to 100 mg IM or IV initially, then 25 mg to 50 mg three to four times/day if necessary.  <u>Preoperative anxiety:</u> On days preceding surgery, 5 mg to 10 mg by mouth three or four times daily. OR 50 mg to 100 mg IM one hour prior to surgery.  <u>Acute alcohol withdrawal:</u> 50 mg to 100 mg by mouth, repeat as needed (up to 300 mg/day). OR 50 mg to 100 mg IM or IV initially, repeat in 2 to 4 hours as needed.	LA

<sup>5</sup> Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at www.thomson-thomson.com

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Xibrom	Bromfenac Sodium Ophthalmic Solution: 0.1%	One drop in the affected eye(s) twice daily for 2 weeks.	
Xyrem	Sodium Oxybate Oral Solution: 500 mg/mL	Starting dose is 4.5 grams/day divided into 2 equal doses. Dose is taken at bedtime and again 2.5 to 4 hours after first dose. Maximum dose is 9 grams/day.	SA
Zyban	Bupropion HCl Extended-release Tablets: 150 mg	150 mg by mouth twice daily for 7-12 weeks. Maximum dose is 300 mg/day.	SA

\*Frequently used, not all-inclusive.  
\*\*LA (look-alike), SA (sound-alike)  
\*\*\*Name pending approval. Not FOI releasable.

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Xibrom were discussed by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Xibrom with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 124 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Xibrom (see page 5). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
<p>Outpatient RX:</p> <p><i>Xibrom</i>  <i>+ gtt ou bid</i>  <i>#1</i></p>	<p>Xibrom  One drop to both eyes twice a day  Dispense 1</p>
<p>Inpatient RX:</p> <p><i>Continue Xibrom + gtt ou bid until d/c</i></p>	

2. Results:

One respondent in the verbal prescription study interpreted the proposed name as Zyban. Zyban is a currently marketed U.S. drug product. See appendix A for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Xibrom, the primary concerns related to look-alike and sound-alike confusion with Librium, Xyrem, and Zyban. Similarly, through independent review, one additional drug name, <sup>\*\*\*</sup>, was also determined to have potential for confusion with Xibrom.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was confirmation that Zyban could be confused with Xibrom as one respondent from the verbal prescription study misinterpreted the name as Zyban. Although there are limitations to the predictive value of these studies, primarily due to sample size, we have acquired safety concerns due to the positive interpretation with this drug product. A positive finding in a study with a small sample size may indicate a high risk and potential for medication errors when extrapolated to the general U.S. population. The remaining responses were misspelled/phonetic interpretations of the proposed name.

1. Librium may look similar to Xibrom when scripted. Librium contains chlordiazepoxide HCl and is indicated for the treatment of anxiety disorders, symptoms of acute alcohol withdrawal, and preoperative apprehension and anxiety. It is a schedule IV drug that is available in 5 mg, 10 mg, and 25 mg capsules and as a 100 mg powder for injection. Librium can be given orally, intramuscularly or intravenously in doses ranging from 5 mg to 100 mg depending on the route of administration. The letter "L" in Librium can look similar to the letter "X" if the pen is dragged when crossing the letter "X". Librium and Xibrom share the letters i, b, and r in the second, third and fourth positions, respectively. Both names also have the letter "m" as the last letter in each name. The letter "o" can look similar to the letter "u" if it is not prominent. Librium and Xibrom do not share any overlapping product characteristics. They both will be available in different strengths (5 mg, 10 mg, 25 mg, and 100 mg/amp vs. 0.1%), and they both have different indications for use (anti-anxiety and

\*\*\* NOTE: This consult contains proprietary and confidential information that should not be released to the public.\*\*\*

alcohol withdrawal vs. ophthalmic anti-inflammatory), usual dose (5 mg to 100 mg vs. one drop), route of administration (oral, IM or IV vs. topical), dosing interval (TID or QID vs. BID), and dosage form (capsules or powder for injection vs. ophthalmic solution). Although Librium and Xibrom share orthographic similarities, the lack of overlapping product characteristics will decrease the potential for confusion between the two drug products.

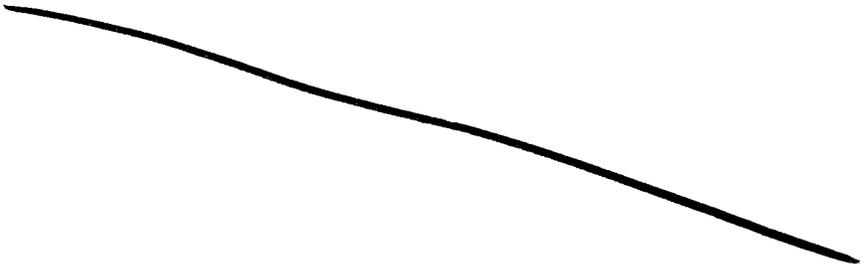
Librium

*Librium*

Xibrom

*Xibrom*

2. Xyrem may sound similar to Xibrom. Xyrem is a schedule III drug that contains the active ingredient sodium oxybate. It is an oral solution indicated for the treatment of cataplexy in patients with narcolepsy. The recommended starting dose is 4.5 g/day divided into two equal doses. Xyrem must be taken at bedtime while the patient is in bed, and again 2½ to 4 hours after the first dose. The maximum dose is 9 g/day. The oral solution is available at a concentration of 500 mg/mL. Xyrem sounds similar to Xibrom because each name contains two syllables and the first syllable of each name is phonetically identical (“Xy” vs. “Xi”). The second syllable is similar (“rem” vs. “brom”), as the “b” sound can be inaudible if it is not prominently enunciated. Although Xyrem and Xibrom are dosed twice daily, Xyrem is more specific with the timing in which each dose must be given. For example, Xyrem must be taken at bedtime while the patient is in bed, and again 2½ to 4 hours later. Xibrom does not have the same dosing time constraints. The products differ in strength (500 mg/mL vs. 0.1%), indication for use (narcolepsy vs. ophthalmic anti-inflammatory), usual dose (4.5 g to 9 g vs. one drop), route of administration (oral vs. topical), and prescriber population. Both Xyrem and Xibrom are available as solutions, however, Xyrem is an oral solution, and Xibrom is an ophthalmic solution that will be dispensed in a dropper bottle. DMETS believes that despite the phonetic similarities, the differentiating product characteristics will minimize the risk of confusion and error between Xyrem and Xibrom.
3. Zyban may sound similar to Xibrom. Zyban contains bupropion hydrochloride and is indicated as an aid to smoking cessation treatment. It is available as a 150 mg extended-release tablet. The usual dose is 150 mg twice daily. Zyban and Xibrom contain two syllables. The first syllable of each name sounds identical (“Zy” vs. “Xi”). The second syllable has a slight phonetic similarity (“ban” vs. “brom”), however, the short “a” sound in Zyban and the soft “r” in Xibrom helps to distinguish the names. The products share an overlapping dosing interval (twice daily) and they are available only in one strength (150 mg vs. 0.1%); otherwise, they differ in indication for use (smoking cessation vs. ophthalmic anti-inflammatory), usual dose (150 mg vs. one drop), route of administration (oral vs. topical), dosage form (tablets vs. solution), and prescriber population. Furthermore, Xibrom will be used for two weeks, whereas Zyban is used for a period of 7-12 weeks. DMETS believes that the minimal sound-alike similarities and the product differences make it unlikely that Zyban and Xibrom will be confused for one another.
4. \_\_\_\_\_



### III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Xibrom, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

#### A. GENERAL COMMENT

Draft copies of the labels and labeling were provided in black and white, and may not represent the true color of the labels and labeling. It is not possible to fully assess the safety of the labels and labeling because the information provided did not reflect the label and labeling presentation that will actually be used in the marketplace (i.e. color, placement of name, design, etc.). Please forward copies of the final printed labels and labeling when they are available.

#### B. CONTAINER LABEL

1. See GENERAL COMMENT.
2. Ensure the NDC # is located in the top third of the principal display panel as described in CFR 207.35(3)(i).
3. Increase the prominence of the established name and strength.
4. If space permits, include the “each mL contains...” statement.

#### C. CARTON

1. See GENERAL COMMENT.
2. See comment B2.

#### IV. RECOMMENDATIONS:

- A. DMETS has no objections to the use of the proprietary name Xibrom. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document.
- B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review that might lead to safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.
- C. DDMAC finds the proprietary name Xibrom acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

---

Felicia Duffy, RN  
Safety Evaluator  
Division of Medication Errors and Technical Support  
Office of Drug Safety

Concur:

---

Alina Mahmud, RPh  
Team Leader  
Division of Medication Errors and Technical Support  
Office of Drug Safety

Appendix A. Xibrom Prescription Study Results

<b>Written Inpatient</b>	<b>Written Outpatient</b>	<b>Verbal</b>
Xibirm	Xebicorn	Cibrom
Xibrim	Xebriom	Cybalt
Xibrim	Xibrom	Cybrom
Xibrim	Xibrom	Cybrom
Xibrim	Xilicom	Cybrom
Xibrim	Xilicom	Cybrom
Xibrim	Xilicom	Cyrom
Xibrim	Xilicom	Fibrom
Xibrim	Xilicom	Fibrom
xibrim	Xilicrom	Psybrom
Xibrim	Xilirom	Sidebrom
Xibrim	Xilirom	Xelirom
Xibrim	Xilirom	Xybrom
Xibrim	Xilirom	Zyban
Xibrom	Xilirom	Zybrom
Xibrom	Xiliron	Zybrom
Xibson	Xilisom	Zybrom
Xibum	Xiluom	Zybrom
Xibum	Xiluom	Zybrom
Xisrim		Zybrom
		Zyprom
		Zyrom

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

-----  
Felicia Duffy  
7/6/04 03:26:24 PM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
7/7/04 01:48:48 PM  
DRUG SAFETY OFFICE REVIEWER

**PRESCRIPTION DRUG  
USER FEE COVER  
SHEET**

**See Instructions on Reverse Side Before Completing This Form**

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS

Marvin J. Garrett  
ISTA Pharmaceuticals, Inc.  
15279 Alton Parkway  
Suite 100  
Irvine, CA 92618

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER  
021-664

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?  
 YES  NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

NDA 21-664

(APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER (Include Area Code)

( 949 ) 788-5303

3. PRODUCT NAME

XIBROM : (Bromfenac Sodium Ophthalmic Solution) 0.1%

6. USER FEE I.D. NUMBER  
4776

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)

A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See item 7, reverse side before checking box.)

THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (See item 7, reverse side before checking box.)

THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES  NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
Food and Drug Administration  
CBER, HFM-99  
1401 Rockville Pike  
Rockville, MD 20852-1448

Food and Drug Administration  
CDER, HFD-94  
and 12420 Parklawn Drive, Room 3046  
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE

*Paul D. Krause for*

TITLE

VP, Regulatory Affairs, Quality & Compliance

DATE

5/19/2004

### **1.3.6 Financial Disclosure Information**

This section provides financial disclosure information for the US Phase III study included in this application as required by the United States Code of Federal Regulations Title 21 Part 54. A copy of Form FDA 3454 certifying the absence of financial interests for investigators who supplied data used in that clinical study in support of this application is provided in Section 1.3.6.1. A list of investigators covered by the statement is provided directly behind the form.

The other clinical studies included in this application were sponsored by Senju Pharmaceutical Co., Ltd. and were conducted in Japan. ISTA Pharmaceuticals, Inc. did not collect financial disclosure information from the investigators in those studies.

### CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See attached lists.	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Lauren P. Silvermail	TITLE Chief Financial Officer and Vice President Corporate Development
FIRM/ORGANIZATION ISTA Pharmaceuticals, Inc.	
SIGNATURE <i>Lauren P. Silvermail</i>	DATE 25 March 2004

#### Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14C-03  
Rockville, MD 20857



**MEMORANDUM OF MEETING MINUTES**

**MEETING DATE:** April 9, 2004  
**SCHEDULED START TIME:** 2:00 pm  
**START TIME:** 2:05 pm  
**END TIME:** 2:30 pm  
**LOCATION:** 9201 Corporate Boulevard  
Rockville, MD 20850

**APPLICATION:** IND 60,295  
**DRUG:** Xibrom (bromfenac sodium hydrate ophthalmic solution)  
0.1% Sterile ophthalmic solution  
**INDICATION:** for the treatment of postoperative inflammation in patients  
who have undergone cataract extraction  
**SPONSOR:** ISTA Pharmaceuticals

**TYPE OF MEETING:** Pre-NDA Meeting

**MEETING CHAIR:** Wiley A. Chambers, MD

**MEETING RECORDER:** Raphael R. Rodriguez

**FDA Attendees:** Wiley Chambers, Brian Harvey, William Boyd, Jennifer Harris, Martin Nevitt, Rhea Lloyd, Linda Ng, Yong deLu, Chandra Chaurasia, Asoke Mukherjee, Josie Yang, Lin Qi, Stephen Langille, Lori Gorski, Raphael Rodriguez

**ISTA Attendees:** William Craig, Marvin Garrett, Paul Krause  
**ISTA Teleconference Attendees:** Lisa Grillone, Kirk McMullin, Mashid Zahed, Tara Creaven, Jean Siegel, Vince Anido, Tom Mitro, Lugo Nelson, Cynthia Hartstein

**MEETING OBJECTIVE:** To discuss to discuss the NDA filing for Xibrom (bromfenac sodium hydrate ophthalmic solution) 0.1% for treatment of postoperative inflammation in patients who have undergone cataract extraction.

## 1. Pharmacokinetics

We have a follow-up question about the following recommendation regarding clinical pharmacokinetic data:

*The Agency recommends providing the complete PK profile ( $C_{max}$ ,  $AUC_{0-t}$ ,  $AUC_{0-inf}$ ,  $t_{1/2}$ ,  $t_{max}$  and  $Ke$  values) obtained in the study reports F-27 and G-01 with the NDA submission.*

The F-27 study report (provided in IND volume 19, pp 13-55) includes whole blood and plasma radioactivity concentrations following oral administration of 50 mg of  $^{14}C$ -bromfenac by subject and  $C_{max}$ ,  $t_{max}$ , AUC, and  $t_{1/2}$  values by subject and mean values across all 6 subjects (Tables 2-8 in the report text). These parameters were calculated by noncompartmental methods using the LAGRAN program. In addition, we will provide in the NDA the parameters requested by FDA calculated using WinNonlin version 2.1

All of the available information for G-01 was provided in the study report that was included in the IND (volume 19, pp 56-77). The concentration of bromfenac sodium in the blood at specified times during treatment with two drops of 0.1% or 0.2% bromfenac sodium ophthalmic solution 4 times daily for 28 days was less than the HPLC detection limit at each time it was measured. The measurement times were 15 minutes, 30 minutes, 1 hour, and 2 hours after single-dose instillation, 4 hours after instillation on Day 14, 16 hours after instillation on Day 28, and 1 and 4 hours after the final dose. The pharmacokinetic parameters the FDA requested therefore cannot be provided for this study.

As stated in FDA's minutes, the predicted peak plasma levels of an ophthalmic dose of a 0.1% solution would be far lower than those measured in the oral administration study. We believe these data support the conclusion that an additional PK study is not needed for the NDA but, based on this response to FDA's additional recommendation, would like to confirm this.

**FDA Response:** *Based on the information provided in IND 60,295/N014 submission dated 08/12/2003, the Agency confirms that additional PK study is not recommended at this point for the submission of NDA on ISTA's bromfenac, sodium hydrate ophthalmic solution, 0.1%. However, NDA approval is a review issue, and the Agency would make any further recommendation(s) on pharmacokinetic studies, if needed, only after reviewing the data from Study Report F-27, that the Sponsor plans to provide with the NDA submission. The sponsor is requested to include all relevant data including those for analytical method validations in the NDA submission for PK studies' reports F-27 and G-01.*

## 2. Nonclinical Summary

For the Module 2 safety summaries of nonclinical data, we propose listing all of the nonclinical study reports in the appropriate CTD overview tables. We propose to provide individual report CTD-format tables only for the 20 studies performed by Senju plus the Wyeth-Ayerst in vitro protein binding study (based on FDA's specific request for data on plasma protein binding, reflected in the meeting minutes). Because the Wyeth-Ayerst studies were reviewed for their NDA that supported approval of the oral formulation, we propose to summarize all other

Wyeth-Ayerst data in the text but not to create new CTD-format tables for those studies. Is this approach acceptable?

**FDA Response:** *Acceptable*

### **3. Clinical - Handling of Japanese Clinical Data**

As discussed at the pre-NDA teleconference, the reports of supportive Japanese clinical trials will be provided in the NDA. In the clinical summary and overview, we will address safety and efficacy results of these supportive studies but the data will not be integrated with the US phase 3 data. Datasets are not available for these supportive studies. Please confirm that this approach is acceptable.

**FDA Response:** *Acceptable. Per the bromfenac Pre-IND meeting minutes of July 23, 2001, the Agency expects full study reports on previous investigations with bromfenac for review by the agency to support the NDA submission.*

### **4. General Format**

The Table of Contents will include CTD headings/subheadings for sections that are not applicable to this NDA and identify them there as “*not applicable.*” For these sections we do not plan to include tab identifiers and text saying they are not applicable in the body of the submission. Is this acceptable?

**FDA Response:** *No. Prefer that these sections include tab identifiers and text saying they are not applicable in the body of the submission.*

In the comprehensive Table of Contents and each module Table of Contents we propose to include all numbered headings that are used in the NDA documents, which may involve going beyond the 5<sup>th</sup> level in some cases (e.g., in quality Module 3). We recognize that ICH CTD guidance identifies a specific level of “granularity” but we believe that a complete Table of Contents is most useful to reviewers. Please confirm that this approach is acceptable.

**FDA Response:** *Agree. A complete Table of Contents is most useful.*

### **5. Acceptability of Trade Name: XIBROM™**

Is the trade name XIBROM™ acceptable to the FDA?

**FDA Response:** *The proposed trade name has been forwarded to DMETS (Division of Medication Errors and Technical Support) for evaluation.*

### **6. Status on the Waiver of Pediatric Patients**

A waiver was requested on the basis [(21CFR314.55(c)(2)(i) and 21 CFR 201.57(a)(9)] that the drug product does not represent a meaningful therapeutic benefit over existing treatments for

pediatric patients (age 16 and younger) and is not likely to be used in a substantial number of pediatric patients. Does the FDA agree that a waiver for pediatric patients is appropriate?

**FDA Response:** *Agree.*

*For the proposed indication, treatment of post-operative inflammation in patients who have undergone cataract extraction, the drug product does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and is not likely to be used in a significant number of pediatric patients.*

#### **7. CMC - Module 3 Table Identification**

Regarding identification of data tables within the body of the subsections, we propose to label the tables as follows. In Section 3.2.S.7.3 entitled Stability Data, for example, the first table will be labeled Table 3.2.S.7.3-1, the subsequent table will be labeled Table 3.2.S.7.3-2 and so forth. Is this acceptable?

**FDA Response:** *Acceptable.*

#### **8. CMC - Module 3 Document Location**

Regarding the placement and location of protocols and associated reports, it is not clear from the CTD Guidance Documents where the attachments should be placed in this module. We propose to place the attachments in the relevant section directly after the narratives describing the relevant section. In Section 3.2.S.6 Container Closure System, for example, we would provide the dimensional drawings as Attachment 3.2.S.6-1 immediately following the narratives describing the container closure system. Is this acceptable?

**FDA Response:** *Acceptable.*

#### **9. Number of Copies**

We also have one additional general question based on information in FDA's August 2001 guidance on "Submitting Marketing Applications According to the ICH-CTD Format – General Considerations." The guidance recommends that the sponsor contact the Division to determine how many copies of each module or sections of modules should be submitted. We would appreciate the Division's feedback on the proposal shown in Table 1 regarding number of copies for submission, which is provided in Attachment 2. (Note: we have added in this submission the row for hard copy submission of case report forms and patient profiles [tabulations].)

**FDA Response:**

*Module 1 and Module 2: submit 24 copies of each (module typically only 1 jacket in length). Six of the jackets should be color coded and submitted as reviewer copies (tan, red, green, white, yellow, & orange); the rest as should be submitted as desk copies sent to the P.M. (no specific color jacket).*

*Module 3: submit two copies; a red-jacketed copy for CMC and a white-jacketed copy for micro-sterility. The field copy should be sent directly to the district office.*

*Module 4: submit one yellow -jacketed copy for Pharm/Tox.*

*Module 5: submit two copies; one tan-jacketed for clinical reviewer and one green-jacketed for statistical reviewer. Additionally, Module 5 should include the PK section which is usually not more than 1 jacket in length.*

*It is not necessary for the PK reviewer to receive the clinical portion of Module 5. It is necessary for the clinical reviewer to receive the PK section. The PK reviewer copy should be orange-jacketed.*

#### **10. CRFs and CRTs**

Regarding Case Report Forms (CRFs) and Case Report Tabulation (CRTs), we are in the process of evaluating a paper versus an electronic submission. We have not yet finalized our decision but will inform the Agency as soon as possible.

Regarding Case Report Forms, in lieu of submitting 100% of the patient CRFs, we propose to submit CRFs only for those patients who experienced serious adverse events, discontinuance and deaths, if any. Is this acceptable to the Agency?

**FDA Response:** *Acceptable. The CRFs for subjects experiencing serious adverse events, discontinuance for any reason, or deaths should be submitted. Whether submitted in paper or electronic format, the CRFs should be properly organized and indexed so they can be easily located.*

#### **11. CMC – Source Documents from Japan**

Regarding drug substance and in preparation for Pre-approval Inspection, specifically supportive stability data from Senju Pharmaceuticals studies, will the Agency require that the source documents from Japan e.g. laboratory notebooks be available at the time of inspection, or will the tabulated data which will be provided in the Senju DMF meet the inspection requirement?

**FDA Response:** *All tabulated data provided in the Senju DMF will only be used to support the review of the Senju's DMF. However, both tabulated data and source documents generated by Senju Pharmaceuticals of Japan should be available at Senju Pharmaceuticals at the time of inspection.*

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this page is the manifestation of the electronic signature.**  
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/s/

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Wiley Chambers  
5/4/04 11:15:41 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

PIND 66,913

ISTA Pharmaceuticals, Inc.  
Attention: Marvin Garrett  
VP Regulatory Affairs, Quality and Compliance  
15279 Alton Parkway  
Suite 100  
Irvine, CA 92618

Dear Mr. Garrett:

Please refer to the Pre-NDA meeting between representatives of your firm and FDA on April 9, 2004. The purpose of the meeting was to discuss the NDA filing for Xibrom (bromfenac sodium hydrate ophthalmic solution) 0.1% for treatment of postoperative inflammation in patients who have undergone cataract extraction.

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

If you have any questions, call Raphael R. Rodriguez, Regulatory Project Manager, at (301) 827-2090.

Sincerely,

*{See appended electronic signature page}*

Wiley A. Chambers, M.D.  
Deputy Director  
Division of Anti-Inflammatory, Analgesic  
and Ophthalmic Drug Products, HFD-550  
Office of Drug Evaluation V  
Center for Drug Evaluation and Research

Enclosure

**August 12, 2003**

**IND 60,295 Bromfenac Sodium Hydrate Ophthalmic Solution 0.1%**

**Pre-NDA Teleconference Meeting Minutes**

**FDA Attendees:** Wiley Chambers, Jonca Bull, Brian Harvey, William Boyd, Matt Feinsod, Josie Yang, Conrad Chen, Chandra Chaurasia, Linda Ng, Gary Gensinger, John O'Malley, Lori Gorski, Mike Puglisi, Raphael Rodriguez

**ISTA Attendees:** Vicente Anido, John Chandler, William Craig, Marvin Garrett, Lisa Grillone, Kirk McMullin, Takahiro Ogawa

**Consultant:** \_\_\_\_\_

**NDA 21-664** has been assigned. Expected arrival March 2004.

**Proposed Indication**

Treatment of post-operative inflammation in patients who have undergone cataract extraction.

**Nonclinical and Pharmacokinetics Questions**

1. Does the FDA agree that additional pharmacokinetic studies using a more sensitive plasma assay are not required for NDA approval for this ophthalmic product?

***FDA Response: Agree.***

*The firm has reported pharmacokinetic study F-27 using 50-mg oral dose in healthy subject that resulted in a C<sub>max</sub> of 4.87+ 1.78  $\mu$ g.eq/mL. Additionally, in the study G-01 involving ophthalmic instillation of 0.1 or 0.2% bromfenac solution—single dose and 2 drops QID for 4 weeks in healthy volunteers—no detectable plasma levels of bromfenac could be observed. It was earlier noted by the Agency that the analytical assay method used in this study was relatively insensitive to that of the published ones.*

*The reported oral bioavailability, plasma half-life and volume of distribution of bromfenac are 67%, 1.3 hr, and 0.15 L/kg, respectively \_\_\_\_\_*

*Assuming 100% bioavailability, the predicted peak plasma levels of a single (one drop) and multiple (1 drops into each eye twice daily for 7 days) ophthalmic dose of a 0.1% solution would be approximately 10- and 280 ng/mL, respectively not considering metabolism and clearance. These levels are still far lower than that measured in the oral study. The Agency, therefore, agrees that additional pharmacokinetic studies using a more sensitive plasma assay are not required for NDA approval for this product.*

2. Does the FDA agree that the nonclinical and pharmacokinetic data as submitted in the original IND (available reports and cross-references to the Duract NDA) are sufficient to support NDA approval for this ophthalmic product?

**FDA's Response:** *From Clinical Pharmacology and Biopharmaceutics perspective, the PK data in the original IND are sufficient to accept an NDA submission, however, NDA approval is a review issue.*

From nonclinical prospective, the data submitted in the IND are sufficient for the NDA submission. (CHC)

3. If further clinical pharmacokinetic data are required, could the analysis be limited to plasma concentrations of bromfenac only since the majority of the circulating drug is unchanged and the expected plasma concentration is quite low (ng/mL)?

**FDA's Response:** *Please see response to Q1 above. At this point, the Agency does not recommend additional PK study.*

**Additional recommendations:**

- *The Agency recommends providing the complete PK profile (C<sub>max</sub>, AUC<sub>0-t</sub>, AUC<sub>0-inf</sub>, t<sub>1/2</sub>, t<sub>max</sub> and K<sub>e</sub> values) obtained in the study reports F-27 and G-01 with the NDA submission.*
- *Agency recommends providing results from plasma protein binding.*

**Clinical Questions**

4. Response/discussion of ISTA's June 20th submission responding to FDA's April 22<sup>nd</sup> clinical questions.

**FDA Response:** *Per the M.O. Review dated July 10<sup>th</sup>:*

- i. *The summed score of 0 at 14 days refers to findings that are less than one (i.e., 1-5 cells) in acceptable grading systems of both cell and flare. The Nussenblatt grading system for cells and the Hogan system for flare are acceptable grading systems.*

*Per the bromfenac Pre-IND meeting minutes of July 23, 2001, the test drug must show statistical and clinical superiority to placebo. Based on the proposed five (5) point scales for cell and flare, a minimum of 1-point difference between test drug and placebo must be demonstrated to show clinical significance.*

*As described in the original protocol submission, the primary efficacy variable will demonstrate statistical significance but not necessarily clinical significance.*

- ii. *If a single large Phase 3 trial is to be "split" and analyzed as two separate trials, the agency **strongly suggests** that the sites be apportioned geographically, e.g. sites East of the Mississippi versus West of the Mississippi.*

*The statistical plan for "splitting" the two groups should be formally submitted to the agency as soon as possible for additional comment and review. The plan should be submitted prior to enrollment.*

- iii. *Per the bromfenac Pre-IND meeting minutes of July 23, 2001, full study reports on previous investigations with bromfenac should be submitted for review by the agency to support an NDA submission.*

5. Assuming that the 2 analyses of US Phase 3 data (each including 21 study sites) each demonstrate statistically and clinically significant superiority of bromfenac compared with placebo for efficacy and an acceptable safety profile, does the FDA agree that these clinical data will be adequate and sufficient for NDA approval?

*FDA Response: Approvability is a review issue and would come after review of an entire NDA. Assuming the M.O. concerns regarding ISTA-BR-CS001 are adequately addressed, the "split" trial should serve as two adequate and well controlled trials.*

6. Does the Agency concur that the proposed information for the Japanese clinical studies will be adequate for these supportive clinical data in the NDA?

*FDA Response: The proposed additional information (in addition to the study reports) for the Japanese clinical trials appears acceptable.*

### **CMC Questions**

7. Is the proposed plan regarding stability data acceptable to the Agency for the NDA submission?

*FDA Response: Yes, the data as proposed can be submitted at NDA submission. However, we prefer to have [REDACTED] primary stability data according to ICH Q1A guidance*

8. If [REDACTED] room temperature data and accelerated stability data as described are available at the time of NDA approval, would the [REDACTED] data from Senju be sufficient to support approval of [REDACTED] expiration dating for the product?

***FDA Response:***

*Senju's data can be submitted as supporting stability data at NDA submission. However, the acceptability of Senju's data to support the proposed expiry is a review issue.*

*It is recommended that additional stability data should be submitted early in the review cycle, not later than [REDACTED] but preferably within [REDACTED]. Data submitted late may not be reviewed in that cycle.*

*Based on the amount of proposed data and the timing of submitted data, granting of [REDACTED] expiry is not likely.*

9. ISTA intends to submit data for three registration stability batches. The batch size for the registration stability batches will be approximately [REDACTED] each. These batches will be manufactured in the production facility, using the same systems and processes as will be used for commercial manufacture. The expected batch sizes for commercial manufacture will be from [REDACTED]. Prior to commercialization, ISTA will manufacture three process validation batches and will place these batches into both accelerated and real-time stability. The process validation protocol and stability protocols will be submitted in the NDA. A process validation report will be approved by Bausch & Lomb and ISTA prior to commercialization of drug product. Is this approach acceptable to the Agency?

*FDA Response: Acceptable*

#### **NDA Format Questions**

10. Does the Division recommend that this NDA be formatted specifically following the CTD guidelines for all modules or are there other or additional recommendations regarding the NDA format?

*FDA Response: The NDA should follow the CTD format for all modules. Section 5.3.5.3 should contain the equivalent information of the ISE and ISS.*

11. Is the proposed location of CMC information for the clinical trial material manufactured at [REDACTED] in Module 2, Section 2.3.P.2 and Module 3, Sections, 3.2.P.2.2.1 and 3.2.P.2.3 acceptable?

*FDA Response: Yes.*

#### **Additional comment:**

*Chemistry did not have a chance to review the email inquiries received the morning of the meeting. All inquiries should be submitted formally with a request for response.*

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this page is the manifestation of the electronic signature.**  
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/s/

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Wiley Chambers  
9/5/03 04:44:10 PM

-----Original Message-----

**From:** Rodriguez, Raphael R  
**Sent:** Thursday, August 07, 2003 11:41 AM  
**To:** 'mgarrett@istavision.com'  
**Cc:** Rodriguez, Raphael R  
**Subject:** IND 60,295 Submission Date: June 20, 2003

Mary: below are the actual comments of the clinical reviewer. If you have any questions, please call at (301)827-2090. Thanks. Raphael

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**Submission Date: June 20, 2003**

**Drug:** bromfenac sodium hydrate ophthalmic solution

**Submitted:**

Submitted is ISTA's response to FDA Medical Officer comments transmitted to ISTA on April 22, 2003, regarding Protocol C-03-15.

**FDA Issue #1:**

This is a multi-center trial. The curriculum vitae and Form 1572 for any additional investigators should be submitted prior to initiation of the trial.

**ISTA Response:**

ISTA agrees with this comment and, subsequent to the original IND filing, submitted. Form 1572 and CVs for several investigators (Amendments 004, 006, 007, 010 and 111). As new investigators are added to the trial their documentation will be submitted.

**Reviewer's Comments:** *Acceptable.*

**FDA Issue #2:**

The study drug must show both statistical and clinical significance in the reduction of summed ocular inflammation scores (or anterior chamber cell) versus placebo. As described, the primary efficacy variable will demonstrate statistical significance but not necessarily clinical significance. The primary efficacy variable should be changed to either:

- i. patients with summed scores of 0 at 14 days (cleared ocular inflammation) or
- ii. a mean 1-point difference on a five-point scale between treatment groups.

**ISTA Response:**

In the Division's comments on clinical deficiencies (04-22-03), comments are provided about acceptable endpoints. In the comments on the endpoint of summed scores at 14 days, there are references to scores of "zero" and "cleared ocular information [sic]." As well, there is mention in the 1-point difference of a five-point scale (presumably 0 to 4) between treatment groups.

- a. Since all commonly utilized grading systems in the literature recognize that a few cells (usually up to 5) are seen in the aqueous humor of normal eyes and that both flare grading systems acknowledge that a "slight flare" may be seen at normal levels of protein

(approximately 11 mg per 100 mL of aqueous humor), the sponsor believes that "zero" referred to by the agency includes findings that are less than one (i.e., 1-5 cells) in grading systems of either cell or flare. For example, a cell reading of 3 cells would be a grade of "0" while 6 or more cells would be a grade of "1". Similarly, "faint" or "very slight" flare (as seen in normal eyes) would be "0" and "mild flare" would be "1" or less. (The sponsor is using the Nussenblatt grading system for cells and the Hogan system for flare.) Please comment.

b. The sponsor appreciates the comments from the agency regarding significance, both statistical and clinical. It would be most instructive to have the agency's guidance of how clinical significance must be demonstrated for each of the agency's recommended endpoints. Please comment.

**Reviewer's Comments:**

*The summed score of 0 at 14 days refers to findings that are less than one (i.e., 1-5 cells) in acceptable grading systems of both cell and flare. The Nussenblatt grading system for cells and the Hogan system for flare are acceptable grading systems.*

*Per the bromfenac Pre-IND meeting minutes of July 23, 2001, the test drug must show statistical and clinical superiority to placebo. Based on the proposed five (5) point scales for cell and flare, a minimum of 1-point difference between test drug and placebo must be demonstrated to show clinical significance.*

*As described in the original protocol submission, the primary efficacy variable will demonstrate statistical significance but not necessarily clinical significance.*

**FDA Issue #3:**

The agency expects to see two analyses. One, a per-protocol analysis on observed cases only, and the other, an intent-to-treat analysis with last observation carried forward. If results from the two analyses differ, an explanation should be provided.

**ISTA Response:**

The sponsor will provide three analyses of the primary and secondary outcomes. The primary analysis will be an intent-to-treat analysis with the last observation carried forward. Two secondary analyses will be conducted. One analysis will utilize observed data only (i.e., the last observation will not be carried forward for the intent-to-treat population) and the other will utilize the protocol compliant subjects. If the results from the analyses differ, an explanation will be provided.

**Reviewer's Comments:** *Acceptable.*

**FDA Issue #4:**

Demonstration of safety and efficacy to support approval of an NDA will require that at least 2 adequate and well-controlled trials show that the benefits of the drug product outweigh its risks.

**ISTA Response:**

The sponsor has initiated a Phase III placebo controlled study designed to randomize a sufficient number of patients equivalent to the number that would be required in two separate trials. The sponsor will analyze the trial as two separate analyses.

Each site has been assigned drug in blocks of six thus guaranteeing a balance between the treatment and placebo groups within a site. This method of randomization will enable the sponsor to use one randomization sequence for all sites. The sponsor will analyze two groups of 21 sites thus providing two confirmatory analyses equivalent to two separate studies. The first 21 sites along with the second 21 sites (three remain to be identified) to be analyzed, and the respective geographic locations, are provided in an Attachment.

**Reviewer's Comments:**

*If a single large Phase 3 trial is to be "split" and analyzed as two separate trials, the agency strongly suggests that the sites be apportioned geographically, e.g. sites East of the Mississippi versus West of the Mississippi.*

*The statistical plan for "splitting" the two groups should be formally submitted to the agency as soon as possible for additional comment and review. The plan should be submitted prior to enrollment.*

**Additional ISTA Questions:**

With regard to the Japanese data from the post-cataract surgery inflammation trial:

- a. Because the Japanese study compared bromfenac to a non-FDA approved drug (propranolol), we plan to use this as supportive data (presented in a descriptive manner), but we do not plan to integrate these results in the Integrated Summary of Efficacy data. Please comment.
- b. ISTA will provide safety data from only the bromfenac arm of the Japanese study within the Integrated Summary of Safety section but separate from the Phase III safety data. The Japanese safety data will be presented in a descriptive manner only. Please comment.

**Reviewer's Comments:**

*Per the bromfenac Pre-IND meeting minutes of July 23, 2001, full study reports on previous investigations with bromfenac should be submitted for review by the agency to support an NDA submission.*

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/s/

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Raphael Rodriguez  
8/22/03 01:25:27 PM  
CSO

Raphael Rodriguez  
8/22/03 01:27:51 PM  
CSO

# NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

## Application Information

NDA 21-664	Efficacy Supplement Type SE-	Supplement Number
Drug: Xibrom (bromfenac ophthalmic solution) 0.09%		Applicant: ISTA Pharmaceuticals, Inc.
RPM: Raphael R. Rodriguez		HFD-550      Phone # 827-2090
Application Type: <input checked="" type="checkbox"/> 505(b)(1)		Reference Listed Drug (NDA #, Drug name):
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		<b>3S - New formulation</b>
• Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates		
		<b>March 26, 2005</b>
❖ Special programs (indicate all that apply)		
		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		
• OC clearance for approval		
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.		
		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that form FDA-3542 a was submitted.		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted.		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified

<b>Exclusivity (approvals only)</b>	
<ul style="list-style-type: none"> <li>Exclusivity summary</li> </ul>	See attached
<ul style="list-style-type: none"> <li>Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!</li> </ul>	( ) Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	N/A
<b>General Information</b>	
<b>❖ Actions</b>	
<ul style="list-style-type: none"> <li>Proposed action</li> </ul>	(X) AP ( ) TA ( ) AE ( ) NA
<ul style="list-style-type: none"> <li>Previous actions (specify type and date for each action taken)</li> </ul>	
<ul style="list-style-type: none"> <li>Status of advertising (approvals only)</li> </ul>	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
<b>❖ Public communications</b>	
<ul style="list-style-type: none"> <li>Press Office notified of action (approval only)</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> Not applicable
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
<b>❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))</b>	
<ul style="list-style-type: none"> <li>Division's proposed labeling (only if generated after latest applicant submission of labeling)</li> </ul>	3/15/05; <del>3/17/05</del>
<ul style="list-style-type: none"> <li>Most recent applicant-proposed labeling</li> </ul>	3/17/05
<ul style="list-style-type: none"> <li>Original applicant-proposed labeling</li> </ul>	5/24/04
<ul style="list-style-type: none"> <li>Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)</li> </ul>	DMETS 7/7/04 DDMAC 11/16/04
<ul style="list-style-type: none"> <li>Other relevant labeling (e.g., most recent 3 in class, class labeling)</li> </ul>	
<b>❖ Labels (immediate container &amp; carton labels)</b>	
<ul style="list-style-type: none"> <li>Division proposed (only if generated after latest applicant submission)</li> </ul>	3/15/05; <del>3/17/05</del>
<ul style="list-style-type: none"> <li>Applicant proposed</li> </ul>	3/15/05; 3/17/05
<ul style="list-style-type: none"> <li>Reviews</li> </ul>	3/1/505; 3/17/05; 3/18/05
<b>❖ Post-marketing commitments</b>	
<ul style="list-style-type: none"> <li>Agency request for post-marketing commitments</li> </ul>	N/A
<ul style="list-style-type: none"> <li>Documentation of discussions and/or agreements relating to post-marketing commitments</li> </ul>	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	2/11/05; 3/15/05; 3/17/05
❖ Memoranda and Telecons	3/17/05
<b>❖ Minutes of Meetings</b>	
<ul style="list-style-type: none"> <li>EOP2 meeting (indicate date)</li> </ul>	8/12/03
<ul style="list-style-type: none"> <li>Pre-NDA meeting (indicate date)</li> </ul>	4/9/04
<ul style="list-style-type: none"> <li>Pre-Approval Safety Conference (indicate date; approvals only)</li> </ul>	
<ul style="list-style-type: none"> <li>Other</li> </ul>	

<b>Advisory Committee Meeting</b>	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
<b>Summary Application Review</b>	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	N/A
<b>Clinical Information</b>	
❖ Clinical review(s) (indicate date for each review)	3/15/05; 3/18/05 (two)
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	In MSR 3/15/05
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	N/A
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	Requested Waiver (see attachment)
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	12/22/04
❖ Biopharmaceutical review(s) (indicate date for each review)	3/8/05
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
<b>Clinical Inspection Review Summary (DSI)</b>	
• Clinical studies	N/A
• Bioequivalence studies	N/A
<b>CMC Information</b>	
❖ CMC review(s) (indicate date for each review)	3/14/05
<b>Environmental Assessment , completed, see CMC Review</b>	
• Categorical Exclusion (indicate review date)	3/14/05
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	10/18/04; 11/19/04
❖ Facilities inspection (provide EER report)	Date completed: 11/30/04 (X) Acceptable ( ) Withhold recommendation
❖ Methods validation	(X) Completed ( ) Requested ( ) Not yet requested
<b>Nonclinical Pharm/Tox Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	2/4/05
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A