

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**21-664**

**CHEMISTRY REVIEW(S)**

**NDA 21-664**

**XIBROM™  
(bromfenac sodium ophthalmic solution) 0.1035%**

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**ISTA Pharmaceuticals, Inc.**

**Yong-de Lu, Ph.D.  
Division of Anti-inflammatory, Analgesic, and Ophthalmic  
Drug Products**

**HFD-550**



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# Chemistry Review Data Sheet

1. NDA 21-664
2. REVIEW #: 1
3. REVIEW DATE: 14-Mar-2005
4. REVIEWER: Yong-de Lu, Ph.D.

## 24. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
None	

## 24. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	24-May-2004
Amendment	22-Oct-2004
Amendment	03-Nov-2004
Amendment	27-Jan-2005
Amendment	22-Feb- 2005
Amendment	24-Feb- 2005
Amendment	04-Mar-2005
Amendment	09-Mar-2005
Amendment	10-Mar-2005

## 7. NAME & ADDRESS OF APPLICANT:

Name: ISTA Pharmaceuticals, Inc.  
Address: 15279 Alton Parkway, Suite 100  
Irvine, CA 92618  
Representative: Marvin J. Garrett, V.P. Regulatory Affairs, Quality & Compliance  
Telephone: 949-788-5303  
Facsimile: 949-727-0833



## CHEMISTRY REVIEW



### Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: XIBRM™  
b) Non-Proprietary Name (USAN): bromfenac sodium ophthalmic solution 0.1035%  
c) Code Name/#: AHR-10282B  
d) Chem. Type/Submission Priority:  
• Chem. Type: 3  
• Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: N/A

10. PHARMACOL. CATEGORY: Inhibitor for cyclooxygenase 1 and 2. Indicated for the treatment of postoperative inflammation, reduction of eye pain.

11. DOSAGE FORM: Solution

12. STRENGTH/POTENCY: 0.1035%

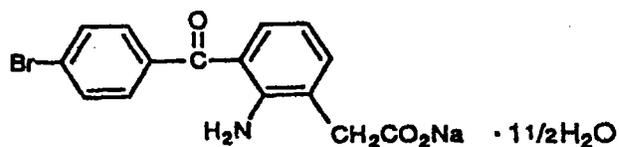
13. ROUTE OF ADMINISTRATION: topical, ocular, one drop per eye twice daily

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:



benzeneacetic acid, 2-amino-3-(4-bromobenzoyl)-, monosodium salt, sesquihydrate  
 $C_{15}H_{11}BrNNaO_3 \cdot 1\frac{1}{2} H_2O$ ; MW = 383.17



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### 17. RELATED/SUPPORTING DOCUMENTS:

#### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
16414	II	Senju Pharmaceuticals	Manufacturer of drug substance	1	Adequate	15-Oct-04	
	III			1	Adequate	06-Mar-03	
	III			3	Adequate	01-Mar-02	USP qualification data are in NDA
	III			3	Adequate	13-Dec-99	no revised information
	III			1	Adequate	24-Feb-03	deficiencies addressed
	III			1	Adequate	06-Mar-03	

<sup>1</sup> Action codes for DMF Table:

- 1 – DMF Reviewed.
- Other codes indicate why the DMF was not reviewed, as follows
- 2 – Type 1 DMF
- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under “Comments”)

<sup>2</sup> Adequate, Inadequate, or N/A (There is enough data in the NDA application, therefore the DMF did not need to be reviewed)



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	60,295 (activated at 3/10/03)	Bromfenac sodium hydrate ophthalmic solution
NDA	20-535 (approved in 1997, suspended in 1998)	DURACT (bromfenac sodium capsules) 25 mg sponsored by Wyeth-Ayerst

### 18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES (3 manufacturing sites)	Overall Accepted	30-Nov-04	
Pharm/Tox	N/A		
LNC			
Methods Validation	Waved		
OPDRA	No comments from DMETS		
EA	Categorical Exclusion		
Microbiology	Approval	18-Oct-04	Stephe Langille

*Appears This Way  
On Original*



## The Chemistry Review for NDA 21-545

### The Executive Summary

#### I. Recommendations

##### A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls perspective, the NDA is recommended for approval.

##### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

#### II. Summary of Chemistry Assessments

##### A. Description of the Drug Product(s) and Drug Substance(s)

XIBROM™ (bromfenac sodium ophthalmic solution) 0.1035% (which is named as Xibrom ophthalmic solution, 0.1035% or Xibrom drug product throughout this review) is a non-steroidal anti-inflammatory drug (NSAID) for ophthalmic use.

Bromfenac was originally developed as an ophthalmic solution by Senju Pharmaceuticals Co., Ltd. in Japan, who licensed this product to ISTA. Phase III development in the U.S. has been conducted under IND 60,295.

Xibrom ophthalmic solution, 0.1035% is supplied as a yellow, buffered, sterile, preserved ophthalmic solution containing 0.1035% bromfenac sodium

The drug product contains bromfenac sodium as the active ingredient, boric acid and sodium borate buffers, disodium edentate and povidone polysorbate 80 sodium sulfite benzalkonium chloride sodium hydroxide for pH adjustment and purified water as a solvent.

Bromfenac sodium as an oral formulation (25 mg capsules) received NDA approval in 1997 (Wyeth-Ayerst NDA 20-535). The distribution of the oral product was voluntarily suspended in 1998 due to hepatotoxicity, which occurred when it was used at levels exceeding the recommended dosage and for prolonged periods of time, resulting in high systemic exposure to the drug.

The drug substance, bromfenac sodium, used in the manufacture of the Xibrom ophthalmic solution, 0.1035% is produced following the methods and controls established in NDA 20-535 by Wyeth-Ayerst.



Executive Summary Section

\_\_\_\_\_ is a contract manufacturer working with Senju Pharmaceuticals. ISTA makes reference to Senju Pharmaceuticals DMF #16414 for the pertinent information required for the drug substance. A letter of authorization dated 5/21/04 authorizing FDA to reference DMF #16414 was attached in Module 1, Section 1.3.7.

The required drug substance information in support of this NDA was also obtained from Wyeth-Ayerst NDA #20-535 in which references were made to bromfenac sodium drug substance produced by \_\_\_\_\_. The relationships among ISTA, Senju, Wyeth-Ayerst \_\_\_\_\_ are discussed in the DMF #16414.

Bausch & Lomb Pharmaceuticals in Tampa, Florida will manufacture the drug product.

The drug product is compounded by dissolving ingredients in purified water, adjusting pH and \_\_\_\_\_

**B. Description of How the Drug Product is Intended to be Used**

The proposed indication for the drug product is for the treatment of postoperative inflammation \_\_\_\_\_ in patients who have undergone cataract extraction.

Xibrom ophthalmic solution, 0.1035% is administered topically to the eye twice a day for up to 14 days. It will be supplied in ophthalmic drop bottles filled to \_\_\_\_\_ (sample size) in nominal \_\_\_\_\_ white \_\_\_\_\_ bottle and \_\_\_\_\_ filled in a nominal \_\_\_\_\_ white \_\_\_\_\_ bottle. The 15 mm sterile white LDPE dropper tip is then inserted into the bottle. A 15 mm sterile gray polypropylene cap is subsequently applied and then the cap is sealed with either \_\_\_\_\_

The drug product is granted 18 months expiration dating period for both configurations.

The product is permitted to be stored at 15 -25°C (59-77°F).

**C. Basis for Approvability or Not-Approval Recommendation**

The NDA submission and amendments has ultimately provided adequate information on the chemistry, manufacturing and controls for the production of Xibrom Ophthalmic Solution, 0.1035%. The \_\_\_\_\_ of the drug substance has been included in the drug product dosage strength, therefore, the strength is \_\_\_\_\_ 0.1035%. The acceptance criteria for assay of benzalkonium chloride and sodium sulfite have been tightened to reflect the actual data observed in the long term stability study of the drug product. The acceptance criterion of NMT \_\_\_\_\_ of any unspecified impurity has been added to the drug product specification. At the time of approval the expiry date is reduced to 18 months \_\_\_\_\_ by ISTA due to insufficient data.



## CHEMISTRY REVIEW



### Executive Summary Section

A Microbiology consult review recommended an approval action. Xibrom ophthalmic solution, 0.1035% is aseptically filled at Bausch & Lomb manufacturing facilities at Tampa, FL. No deficiencies were identified upon the information provided. All manufacturing and testing sites for both drug substance and drug product have been inspected and accepted by Office of Compliance.

### III. Administrative

#### A. Reviewer's Signature

Signed electronically in DFS

#### B. Endorsement Block

Signed electronically by Chemistry Team Leader in DFS

#### C. CC Block

Original NDA 21-664  
HFD-550/CSO/RRaphael

HFD-550/Chem Team Leader/LNg  
HFD-550/MED/WChambers

68 Page(s) Withheld

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Withheld Track Number: Chemistry-1

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**This is a representation of an electronic record that was signed electronically and  
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/s/  
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Yong-De Lu  
3/14/05 11:50:31 AM  
CHEMIST

Linda Ng  
3/14/05 01:05:13 PM  
CHEMIST