

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
203168Orig1s000

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number: 203168
Supporting document/s: 000
Applicant's letter date: 6/5/2012
CDER stamp date: 6/7/2012
Product: Prolensa™: bromfenac ophthalmic solution, 0.07%
Indication: Treatment of inflammation and pain associated
with cataract extraction
Applicant: ISTA Pharmaceuticals, Inc
Review Division: CDER/OAP/Division of Transplant and
Ophthalmology Products
Reviewer: Robeena Aziz, MPH, PhD
Supervisor/Team Leader: Lori Kotch, PhD, DABT
Division Director: Renata Albrecht, MD
Project Manager: Michael Puglisi

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 203168 are owned by ISTA Pharmaceuticals, Inc or are data for which ISTA Pharmaceuticals, Inc has obtained a written right of reference. Any information or data necessary for approval of NDA 203168 that ISTA Pharmaceuticals Inc. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 203168.

TABLE OF CONTENTS

1	EXECUTIVE SUMMARY	4
1.1	INTRODUCTION	4
1.2	BRIEF DISCUSSION OF NONCLINICAL FINDINGS	5
1.3	RECOMMENDATIONS	6
2	DRUG INFORMATION	8
2.1	DRUG: BROMFENAC SODIUM, 0.07%.....	8
2.2	RELEVANT INDS AND NDAs.....	9
2.3	DRUG FORMULATION	9
2.4	COMMENTS ON NOVEL EXCIPIENTS.....	10
2.5	COMMENTS ON IMPURITIES/DEGRADANTS OF CONCERN	11
2.6	PROPOSED CLINICAL POPULATION AND DOSING REGIMEN	11
2.7	REGULATORY BACKGROUND	11
3	STUDIES SUBMITTED.....	11
3.1	STUDIES REVIEWED.....	11
3.2	STUDIES NOT REVIEWED	12
3.3	PREVIOUS REVIEWS REFERENCED.....	12
4	PHARMACOLOGY.....	12
4.1	PRIMARY PHARMACOLOGY	12
4.2	SECONDARY PHARMACOLOGY	12
4.3	SAFETY PHARMACOLOGY	12
5	PHARMACOKINETICS/ADME/TOXICOKINETICS	13
5.1	PK/ADME.....	13
6	GENERAL TOXICOLOGY.....	17
6.1	SINGLE-DOSE TOXICITY	17
6.2	REPEAT-DOSE TOXICITY	18
7	GENETIC TOXICOLOGY	20
7.4	OTHER GENETIC TOXICITY STUDIES.....	20
8	CARCINOGENICITY	20
9	REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY	20
10	SPECIAL TOXICOLOGY STUDIES.....	20
11	INTEGRATED SUMMARY AND SAFETY EVALUATION.....	21
12	APPENDIX/ATTACHMENTS.....	22

Table of Tables

Table 1: List of nonclinical studies conducted supporting bromfenac ophthalmic solution, 0.07% 5

Table 2: Qualitative and quantitative composition of bromfenac ophthalmic solution, 0.07% 10

Table 3: Comparison Table of proposed, approved and nonclinical toxicology study formulation 10

Table 4: List of impurities present in bromfenac ophthalmic solution, 0.07%..... 11

Table 5: Mean ppm of bromfenac in aqueous humor at indicated time after instillation (mean of 2 rabbits at each time-point)..... 13

Table 6: Mean ppm of bromfenac in aqueous humor at indicated time after instillation (mean of 2 rabbits at each time-point)..... 15

Table 7: Mean ppm of bromfenac in aqueous humor at indicated time after instillation (mean of 3 rabbits at each time-point)..... 17

Table 8: Study protocol 19

1 Executive Summary

1.1 Introduction

The sponsor (ISTA Pharmaceuticals, Inc) is submitting this NDA application for bromfenac ophthalmic solution, 0.07% (also referred to bromfenac sodium, or bromfenac in this review). Bromfenac ophthalmic solution 0.07% is a topical, nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of inflammation and pain associated with cataract extraction. Patients will apply one drop to affected eye(s) once daily beginning one day prior to cataract surgery, on the day of surgery, and through 14 days post surgery.

The indication is the same as the currently marketed product, Bromday™ (bromfenac ophthalmic solution) 0.09%, administered once daily (sNDA 021664 for Bromday™ FDA approval on 10/2010) and Xibrom™ administered twice daily (NDA 21644 FDA approval 3/2005). The bromfenac ophthalmic solution 0.07% formulation in the current submission differs from the currently marketed bromfenac 0.09% product in the amounts of bromfenac sodium and its target pH. (b) (4)

The same manufacturer, Regis Technologies, will continue to supply the bromfenac sodium solution.

The oral formulation of bromfenac (Duract capsules) was developed by Wyeth-Ayerst and was approved for marketing under NDA 20 535 in 1997. However, due to clinical findings of hepatotoxicity after marketing, Duract was withdrawn from the market in June 1998.

Bromfenac sodium was licensed to Senju Pharmaceutical Co., Ltd, Osaka, Japan for development as an ophthalmic solution in Japan (Bronuck®; bromfenac sodium ophthalmic solution, 0.1% dosed BID). The Japanese formulation is identical to the US product, with the concentration of the active shown as the salt form (0.1% bromfenac sodium) rather than the free acid (0.09% bromfenac), respectively. Bronuck was approved in Japan in July 2000, and is indicated for the treatment of blepharitis, conjunctivitis, scleritis (including episcleritis) and post-operative inflammation.

Senju conducted non-clinical and clinical studies for bromfenac ophthalmic solution and obtained approval for marketing in Japan in 2000. Senju recently sublicensed bromfenac for ophthalmic use in the United States to ISTA Pharmaceuticals, Inc. The non-clinical studies submitted in this NDA were conducted by Wyeth-Ayerst and Senju Pharmaceuticals. The nonclinical studies to support this NDA application are referenced to the approved products mentioned above.

This indication in the current submission is supported by two clinical trials (Studies Nos. S00124-ER and S00124-WR) to evaluate the efficacy and safety of bromfenac ophthalmic solution 0.07% vs. placebo for the treatment of ocular inflammation and pain associated with cataract surgery.

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.