CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203168Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL TEAM LEADER REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA203168
Drug Name:	Bromfenac 0.07% Ophthalmic Solution
Indication(s):	Treatment of postoperative inflammation and reduction of ocular pain in patients who have undergone cataract surgery
Applicant:	Bausch+Lomb
Date(s):	Stamp date: June 6, 2012 PDUFA date: April 7, 2013
Review Priority:	Standard
Biometrics Division:	DBIV
Statistical Review Team	Primary statistical reviewer: Abel Eshete, PhD Statistical Team Leader: Yan Wang, PhD
Concurring Reviewers:	Daphne Lin, PhD
Medical Division:	Ophthalmology
Clinical Team:	Medical Reviewer: William Boyd, M.D.
Project Manager:	Michael Puglisi

Keywords: anterior chamber cells, anterior chamber flare, ocular inflammation, ocular pain, cataract surgery.

Table of Contents

1 INTRODUCTION/PURPOSE OF REVIEW 4

2 CURRENT NDA203168 PROLENSA (BROMFENAC OPHTHALMIC SOLUTION, 0.07% QD) 4

3 EFFICAY ANALYSIS EVALUATIONS OF 7 APPROVED NDAS FOR THE TREATMENT OF OCULAR INFLAMMATION AFTER CATARACT SURGERY 8

3.1 NDA021664 XIBROM (BROMFENAC OPHTHALMIC SOLUTION, 0.09% BID) FOR THE TREATMENT OF POSTOPERATIVE INFLAMMATION IN PATIENTS WHO HAVE UNDERGONE CATARACT EXTRACTION 9
3.2 NDA021862 NEVANAC (NEPAFENAC OPHTHALMIC SUSPENSION, 0.1% TID) FOR THE TREATMENT OF PAIN AND INFLAMMATION ASSOCIATED WITH CATARACT SURGERY 12
3.3 NDA022212 DUREZOL (DIFLUPREDNATE OPHTHALMIC SOLUTION, 0.05% QID) FOR THE TREATMENT OF INFLAMMATION AND PAIN ASSOCIATED WITH CATARACT SURGERY 15
3.4 NDA021664 BROMDAY (BROMFENAC OPHTHALMIC SOLUTION, 0.09% QD) FOR THE TREATMENT OF POSTOPERATIVE INFLAMMATION AND REDUCTION OF OCULAR PAIN IN PATIENTS WHO HAVE UNDERGONE CATARACT EXTRACTION 19
3.5 NDA200738 LOTEMAX (LOTEPREDNOL ETABONATE OPHTHALMIC OINTMENT, 0.5% QID) FOR THE TREATMENT OF POSTOPERATIVE INFLAMMATION AND PAIN FOLLOWING OCULAR SURGERY 23
3.6 NDA202872 LOTEMAX (LOTEPREDNOL ETABONATE OPHTHALMIC GEL, 0.5% QID) FOR THE TREATMENT OF POSTOPERATIVE INFLAMMATION AND PAIN FOLLOWING OCULAR SURGERY 26
3.7 NDA203491 ILEVRO (NEPAFENAC OPHTHALMIC SUSPENSION, 0.3% QD) FOR THE TREATMENT OF PAIN AND INFLAMMATION ASSOCIATED WITH CATARACT SURGERY 28
3.8 SUMMARY OF FINDINGS ON THE 7 APPROVED NDAS 30
3.8.1 Varied anterior chamber cell grade scores and flare scores were used to evaluate ocular inflammation 30
3.8.2 Varied definitions were used to define "cleared ocular inflammation" 31
3.8.3 Every Approved NDA had subjects whose ocular inflammation was cleared by week 1 (days 7-8) but was not cleared at week 2 (days 14-15) post-surgery 32
3.8.4 Varied time points and analyses were used for the primary endpoint of cleared ocular inflammation 33
3.8.5 Varied information on the efficacy endpoint and results for ocular inflammation were included in labeling 34

4 RECOMMENDATIONS FOR THE CLINICAL STUDIES SECTION OF THE LABELING FOR THE CURRENT NDA203168 PROLENSA 35

LIST OF TABLES

Table 2. 1 NDA203168: Applicant's Efficacy Analysis Results of Phase 3 Studies....6
Table 2. 2 NDA203168: Number of Subjects whose ocular inflammation was cleared (0 cell and no flare) at or prior to Day 8, but was not cleared (cell score or flare score >0) at Day 15 7
Table 2. 3 NDA203168: FDA's Primary Statistical Reviewer's Analysis Results of Phase 3 Studies 8
Table 3.0 List of NDAs Approved in 2005-2012 for post-operative Inflammation after Cataract Surgery…….. 8
Table 3.1. 1 NDA021664 Xibrom: CRF-defined Anterior Chamber Cell Score....10
Table 3.1. 2 NDA021664 Xibrom: CRF-defined Anterior Chamber Flare Score 10
Table 3.1. 3 NDA021664 Xibrom: Efficacy Results of Phase 3 Studies (Subjects who received a rescue therapy were treated as failures) (Randomized Population)....11
Table 3.1. 4 NDA021664 Xibrom: Efficacy Results of Phase 3 Studies (Subjects who received a rescue therapy were treated as successes if their ocular inflammation was cleared)....11
Table 3.1. 5 NDA021664 Xibrom: Number of subjects whose ocular inflammation was cleared (0 cell and no flare) at or prior to Day 8 but was not cleared at Day 15 (cell score or flare score > 0) 12
Table 3.2. 1 NDA021862 Nevanac: Anterior Chamber Cell Score ……..13
Table 3.2. 2 NDA021862 Nevanac: Anterior Chamber Flare Score 13
Table 3.2. 3 NDA021862 Nevanac: Efficacy Results of Phase 3 Studies (ITT population) 13
Table 3.2. 4 NDA021862 Nevanac: Number of subjects whose ocular inflammation was cleared (0 cell and no flare) at or prior to Day 7 but was not cleared (cell score or flare Score > 0) at Day 14....14
Table 3.3. 1 NDA022212 Durezol: Anterior Chamber Cell Score....15
Table 3.3. 2 NDA022212 Durezol: Anterior Chamber Flare Score 15
Table 3.3. 3 NDA022212 Durezol: Applicant's Efficacy Results of Comparing Durezol QID to Vehicle....17
Table 3.3. 4 NDA022212 Durezol: Applicant's Efficacy Results of Comparing Durezol BID to Vehicle....19
Table 3.4. 1 NDA021664 Bromday: Applicant's Efficacy Results of Phase 3 Studies (ITT Population) ……..21
Table 3.4. 2 NDA021664 Bromday: Number of subjects whose ocular inflammation was cleared (0 cell and no flare) at or prior to Day 8 but was not cleared (cell score or flare score > 0) at Day 15 22
Table 3.4. 3 NDA021664 Bromday: FDA's Analysis Results of Phase 3 Studies....22
Table 3.5. 1 NDA200738 Lotemax Ointment: Anterior Chamber Flare Score 23
Table 3.5. 2 NDA200738 Lotemax Ointment: Efficacy Results of Phase 3 Studies (ITT Population)....24
Table 3.5. 3 NDA200738 Lotemax Ointment: Number of subjects whose ocular inflammation was cleared (0 cell count and no flare) at or prior to Day 8 but was not cleared (cell score or flare score > 0) at Day 15 24
Table 3.5. 4 NDA200738 Lotemax Ointment: Efficacy Results of Phase 3 Studies for the Endpoint of Achieving 0 Cell 25
Table 3.6. 1 NDA202872 Lotemax Gel: Efficacy Results of Phase 3 Studies (ITT Population) 26
Table 3.6. 2 NDA202872 Lotemax Gel: Number of subjects whose ocular inflammation was cleared (0 cell) at or prior to Day 8 but was not cleared (cell score > 0) at Day 15 27
Table 3.6. 3 NDA202872 Lotemax Gel: Efficacy Results of Phase 3 Studies for the Endpoint of Achieving 0 Cell and 0 Flare Score....27
Table 3.7. 1 NDA203491 Ilevro: Efficacy Results of Phase 3 Studies (Randomized Population)....28
Table 3.7. 2 NDA203491 Ilevro: Number of subjects whose ocular inflammation was cleared (0 cell and no flare) at or prior to Day 7 but was not cleared (cell score or flare score > 0) at Day 14 29
Table 3.8. 1: Anterior Chamber Cell Grade Scores in 7 Approved NDAs....30
Table 3.8. 2: Anterior Chamber Cell Flare Scores in 7 Approved NDAs....31
Table 3.8. 3: Definitions of Cleared Ocular Inflammation in 7 Approved NDAs....31
Table 3.8. 4: Number of subjects whose ocular inflammation was cleared by week 1 (days 7-8) but was not cleared at week 2 (days 14-15) post-surgery in the 7 approved NDAs....32
Table 3.8. 5: Timing of Primary Endpoint in 7 Approved NDAs....33
Table 3.8. 6: Information of Ocular Inflammation Presented in Labeling for 7 Approved NDAs....35

1 Introduction/Purpose of Review

To provide support for the primary statistical reviewer's recommendation for the labeling, this statistical team leader's review evaluates the analysis of the primary efficacy endpoint of cleared ocular inflammation in the current NDA203168 and compares the analysis to seven previously approved NDAs for the indication of ocular inflammation after cataract surgery.

Specifically, the focus of this review is on the examination of the definition of postoperative ocular inflammation, including its two components of "anterior chamber cell counts and grade scores" and "anterior chamber flare scores", along with the way these individual components were defined and measured, and the determination on the clearance/resolution of ocular inflammation. In addition to the grade and evaluation of ocular inflammation, this review also examines how many time points were included in each application and which time points were considered important in the assessment of efficacy on ocular inflammation. Furthermore for each application, this review also examines whether there were subjects whose ocular inflammation was cleared by week 1 (days 7-8), but was subsequently not cleared at week 2 (days 14-15) post-surgery, and how these subjects were treated in the analysis of the endpoint "cleared ocular inflammation" at days 14-15.

The endpoint of pain resolution is generally a secondary endpoint in these approved NDAs. Information on this endpoint is included in this review for the sake of completeness; however, the statistical team leader has not specifically examined the scales that were scored to evaluate the presence of pain and the resolution of pain. Therefore, the data on pain resolution are taken directly from the clinical and/or statistical reviews. Because the Clinical Studies sections of labeling are presented in their entirety, this review includes whatever information on pain is included in labeling.

The applicant's and the primary reviewer's analyses for the current NDA203168 are presented in Section 2; the analyses for the 7 approved NDAs are presented in Section 3; and Section 4 concludes with the statistical review team's recommendations for the drug labeling for the current NDA.

2 Current NDA203168 Prolensa (bromfenac ophthalmic solution, 0.07% QD)

In support of the efficacy claim, this NDA included two phase 3 studies in subjects who underwent cataract extraction with posterior chamber intraocular lens implantation. These two studies shared a common protocol and a statistical analysis plan and were conducted in the United States. Both studies were randomized, double-masked, multi-center, parallel, and vehicle (placebo)-controlled studies. The major difference between these two studies was: Study 1 included 20 sites in the east region of the United States and Study 2 included 19 sites in the west region of the United States.

Randomization occurred at the screening visit (1 to 8 days prior to surgery). In each study, 220 patients were randomized to receive either bromfenac 0.07% or vehicle in a 1:1 ratio. Subjects

DOCKET ALARM

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.