APPLICATION NUMBER:
21-132

OTHER REVIEW(S)
CLINICAL INSPECTION SUMMARY

DATE: April 15, 2009

TO: Raphael R. Rodriguez, Regulatory Project Manager
William Boyd, Medical Officer
Division of Anti-Infective and Ophthalmic Products

FROM: Jean Mulinde, M.D.
Good Clinical Practice Branch 2
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch 2
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections.

NDA or BLA: 22-427

APPLICANT: Allergan

DRUG: Acuvail® (ketorolac tromethamine ophthalmic solution) 0.45%

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: For the treatment of pain and inflammation following cataract surgery.

CONSULTATION REQUEST DATE: November 5, 2008

DIVISION ACTION GOAL DATE: July 31, 2009

PDUFA DATE: July 31, 2009
I. BACKGROUND:
Acuvail® (ketorolac tromethamine ophthalmic solution) 0.45% is a nonsteroidal anti-inflammatory drug (NSAID). Acuvail® is a new unpreserved formulation of ketorolac tromethamine ophthalmic solution 0.45% (ketorolac 0.45%) that has been developed to enhance the absorption characteristics and improve comfort when administered in the eye, according to the Applicant. Ktorolac 0.45% is dosed less frequently, twice daily, which results in a reduction in the overall daily systemic exposure. The primary changes in ketorolac 0.45% from previously approved formulations include lowering of the pH to improve ocular bioavailability and the addition of carboxymethylcellulose (CMC), which is proposed to have a soothing effect on the eye. The mechanism of action of ketorolac is thought to result from cyclooxygenase inhibition and subsequent decreased prostaglandin biosynthesis. With injury to ocular tissues, as may occur with cataract surgery, prostaglandin synthesis is stimulated and prostaglandins are believed to be mediators of ocular inflammation, pain, and miosis.

Ketorolac 0.45% is supplied in single-use vials and is to be applied to the affected eye(s) twice daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period for the treatment of pain and inflammation following cataract surgery.

To support approval, the Applicant has provided data from two pivotal clinical trials (Protocol 191578-005 and Protocol 191578-006), which they believe provide sufficient evidence for the safety and efficacy of twice-daily dosing of ketorolac 0.45% for 1 day prior to through 2 weeks post cataract surgery.

PROTOCOL NUMBER: 191578-005 “A Multi Center, Double Masked, Randomized Parallel Group Study Evaluating the Safety and Efficacy of a New Formulation of Ktorolac Tromethamine 0.45% Ophthalmic Solution Compared with Vehicle Administered Preoperatively and Twice-Daily Postoperatively for Two Weeks for the Treatment of Anterior Segment Inflammation, Pain, and Inhibition of Surgically Induced Miosis Following Cataract Extraction with Posterior Chamber Intraocular Lens (IOL) Implantation”

The primary efficacy endpoint of this study was the percentage of patients with a summed ocular inflammation score (SOIS) of anterior chamber cell and flare equal to 0 on postoperative Day 14. The SOIS was calculated as the sum of the score for anterior chamber cells and the score for anterior chamber flare in the operative eye using the scoring systems as outlined in the following table.

<table>
<thead>
<tr>
<th>Anterior Chamber Cells</th>
<th>Anterior Chamber Flare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade Score</td>
<td>Cell Count</td>
</tr>
<tr>
<td>0</td>
<td>0 cells</td>
</tr>
<tr>
<td>+0.5</td>
<td>1-5 cells (trace)</td>
</tr>
<tr>
<td>+1</td>
<td>6-15 cells</td>
</tr>
<tr>
<td>+2</td>
<td>16-25 cells</td>
</tr>
<tr>
<td>+3</td>
<td>26-50 cells</td>
</tr>
</tbody>
</table>
Secondary supportive endpoints included:

1. Postoperative pain resolution (i.e. grade of pain=0) at Day 14 (changed to Day 1 in Protocol Amendment 2). At screening and randomization visits, study site personnel will query the patients regarding the presence or absence of pain in the operative eye. In the evening of the Cataract Surgery Day (approximately one hour after the last dose of study medication), twice-daily (approximately one hour after dosing) on Days 1 through Day 13 Post-op, and approximately one hour after the morning dose on Day 14 Post-op, patients will record the severity of their ocular pain and the use of acetaminophen or other analgesics using an Interactive Voice Response System (IVRS). Patients will be asked to rate the severity of the ocular pain they experience in their postoperative eye using the grade scale described in the table below.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Ocular Pain Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Mild</td>
</tr>
<tr>
<td>2</td>
<td>Moderate</td>
</tr>
<tr>
<td>3</td>
<td>Severe</td>
</tr>
<tr>
<td>4</td>
<td>Intolerable</td>
</tr>
</tbody>
</table>

2. Inhibition of surgically-induced miosis as measured by the pupil area at post irrigation and aspiration of the lens.

Safety endpoints included adverse events, visual acuity, biomicroscopy, intraocular pressure, dilated fundus exam, and pregnancy.

PROTOCOL NUMBER: 191578-006 “A Multi Center, Double Masked, Randomized Parallel Group Study Evaluating the Safety and Efficacy of a New Formulation of Ketorolac Tromethamine 0.45% Ophthalmic Solution Compared with Vehicle Administered Preoperatively and Twice-Daily Postoperatively for Two Weeks for the Treatment of Anterior Segment Inflammation, Pain, and Inhibition of Surgically Induced Miosis Following Cataract Extraction with Posterior Chamber Intraocular Lens (IOL) Implantation”

The design of this study was identical to Protocol Number 191578-005.

The sites requested for inspection were the centers with the largest number of enrolled patients in the pivotal studies that had no prior inspection history. While this product is not a new molecular entity, a field inspection of these pivotal studies was important as they support approval for a revised dosage regimen of this newly formulated, preservative free ketorolac formulation. Therefore, verification of data for safety and efficacy, and evaluation of conduct of pivotal studies was considered vital.
II. RESULTS (by Site):

<table>
<thead>
<tr>
<th>Name of CI/Sponsor Location</th>
<th>Protocol #</th>
<th>Inspection Date</th>
<th>Final Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harvey J. Reiser, M.D.</td>
<td>191578-005</td>
<td>01/14/2009-01/20/2009</td>
<td>NAI</td>
</tr>
<tr>
<td>Eye Care Specialists</td>
<td>Site #10007</td>
<td>Site #10007</td>
<td></td>
</tr>
<tr>
<td>703 Rutter Ave.</td>
<td>27 subjects</td>
<td>01/14/2009-01/20/2009</td>
<td></td>
</tr>
<tr>
<td>Kingston, PA 18704</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Louis M. Alpern, M.D.</td>
<td>191578-006</td>
<td>01/06/2009-01/08/2009</td>
<td>NAI</td>
</tr>
<tr>
<td>The Cataract and Glaucoma Center</td>
<td>Site #10027</td>
<td>Site #10027</td>
<td></td>
</tr>
<tr>
<td>4171 N. Mesa Bldg. Suite 100</td>
<td>30 subjects</td>
<td>01/06/2009-01/08/2009</td>
<td></td>
</tr>
<tr>
<td>El Paso, TX 79902</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leonard Gurevich, M.D.</td>
<td>191578-006</td>
<td>01/07/2009-01/14/2009</td>
<td>VAI</td>
</tr>
<tr>
<td>Western New York Eye Center</td>
<td>Site #10013</td>
<td>Site #10013</td>
<td></td>
</tr>
<tr>
<td>301 Sterling Drive</td>
<td>27 subjects</td>
<td>01/07/2009-01/14/2009</td>
<td></td>
</tr>
<tr>
<td>Orchard Park, NY 14127</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations.
Pending = Preliminary classification. Official letter has not issued.

1. Harvey J. Reiser, M.D.
   Eye Care Specialists
   703 Rutter Ave.
   Kingston, PA 18704
   Protocol 191578-005, Site #10007

   a. What was inspected:
   This inspection was conducted in accordance with Compliance Program 7348.811 between 01/14/2009 and 01/20/2009. A total of 27 subjects were screened, 27 subjects were enrolled and 23 completed the study. Records for 27 enrolled subjects were reviewed to verify subject eligibility, primary and key secondary efficacy data, adverse event data, visual acuity, biomicroscopy results, intraocular pressure assessments, dilated fundus exam results, protocol deviations, subject randomization, subject discontinuations, concomitant medication use, and informed consent. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.
b. **General observations/commentary:**
   The inspection of Dr. Reiser's site did not reveal regulatory violations. A Form FDA 483, Inspectional Observations, was not issued.

c. **Assessment of data integrity:**
   Based on the provided Establishment Inspection Report (EIR) for this site and Dr. Reisers's comments to investigator observations made during the inspection and documented in the EIR, data derived from Dr. Reiser's site are considered acceptable.

2. **Louis M. Alpern, M.D.**
   The Cataract and Glaucoma Center
   4171 N. Mesa Bldg, Suite 100
   El Paso, TX 79902
   Protocol 191578-006, Site #10027

   a. **What was inspected:**
      This inspection was conducted in accordance with Compliance Program 7348.811 between 01/06/2009-01/08/2009. A total of 30 subjects were screened, 27 subjects were enrolled and 20 completed the study. Records for 20 enrolled subjects were reviewed to verify subject eligibility, primary and key secondary efficacy data, adverse event data, visual acuity, biomicroscopy results, intraocular pressure assessments, dilated fundus exam results, protocol deviations, subject randomization, subject discontinuations, concomitant medication use, and informed consent. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

   b. **General observations/commentary:**
      The inspection of Dr. Alperns's site did not reveal regulatory violations. A Form FDA 483, Inspectional Observations, was not issued.

   c. **Assessment of data integrity:**
      Based on the provided Establishment Inspection Report (EIR) for this site and Dr. Alpern's comments to investigator observations made during the inspection and documented in the EIR, data derived from Dr. Alpern's site are considered acceptable.

3. **Leonard Gurevich, M.D.**
   Western New York Eye Center
   301 Sterling Drive
   Orchard Park, NY 14127
   Protocol 191578-006, Site #10013

   a. **What was inspected:**
This inspection was conducted in accordance with Compliance Program 7348.811 between 01/07/2009-01/14/2009. A total of 27 subjects were screened, 26 subjects were enrolled and 23 completed the study. Informed consent documents for all subjects were reviewed. The balance of subject records were spot checked for eligibility criteria, primary and key secondary efficacy data, adverse event data, visual acuity, biomicroscopy results, intraocular pressure assessments, dilated fundus exam results, protocol deviations, subject randomization, subject discontinuations, and concomitant medication use. In addition, drug accountability records, IRB approval and dates, and sponsor monitoring records were reviewed. There were no limitations to the inspection.

b. General observations/commentary:
The inspection of Dr. Gurevich’s site revealed regulatory violations. A Form FDA 483, Inspectional Observations, was issued to this investigator, mainly for:

i. Failure to conduct the study according to the signed investigator statement and the investigational plan [21 CFR 312.60]. Specifically, for:

- For all 26 subjects enrolled, pre-operative medications were dosed anywhere from 1 minute to 2 hours 15 minutes earlier than they should have been prior to the cataract surgery (on average 45 minutes earlier than required by the protocol).
- Two subjects (#1174 and #1183) had cataract surgeries on the other eye within 7 days of study eye surgery (protocol required waiting 15 days), so they received medications for the second surgeries that would be considered excluded concomitant medications by the protocol (Acular and topical ophthalmic prednisone).

c. Assessment of data integrity:
The delay between pre-operative dosing and surgery start time for all subjects and use of prohibited medications for two subjects was discussed with Dr. Boyd, the review division clinical reviewer for this application. Dr. Boyd did not feel that the delays between dosing and surgery start would have significantly impacted either efficacy or safety outcomes for subjects; therefore, while the CI will be sited for this regulatory violation it appears that outcome data from subjects may still be considered reliable. Regarding the two subjects (#1174 and #1183) that received concomitant prohibited medications, DSI recommends that efficacy data for these subjects be excluded from per protocol analyses as use of these medications may have affected efficacy outcome assessments.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three clinical investigator inspections have been completed for this NDA. Based on the results of these inspections, the study appears to have been conducted adequately and the data in support of the NDA appear reliable (with the exception of data from two subjects at Dr. Gurevich’s site).
No regulatory violations were noted for Dr. Reiser or Dr. Alpern.

A Form FDA 483 was issued to Dr. Gurevich. However, based on DSI’s discussion of the issues with the review division it appears that the nature of the violations makes it unlikely that they significantly affect overall reliability of safety and efficacy data from this site, with the exception of data from two subjects (#1174 and #1183). These subjects received prohibited concomitant medications when they had cataract surgery on the other eye within 7 days of study eye surgery. Therefore, DSI recommends that efficacy data for these two subjects be excluded from per protocol analyses as use of these medications may have affected efficacy outcome assessments.

[See appended electronic signature page]

Jean M. Mulinde, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

[See appended electronic signature page]

Tejashri Purohit-Sheth, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jean Mulinde
4/17/2009 12:16:06 PM
MEDICAL OFFICER

Tejashri Purohit-Sheth
4/17/2009 03:52:20 PM
MEDICAL OFFICER
Date: July 21, 2009

To: Wiley Chambers, MD, Acting Director
Division of Anti-Infective and Ophthalmologic Products

Through: Kellie Taylor, PharmD, MPH, Team Leader
Denise Toyer, PharmD, Deputy Director
Carol A. Holquist, RPh, Director
Division of Medication Error Prevention and Analysis

From: Felicia Duffy, RN, BSN, MSEd, Safety Evaluator
Division of Medication Error Prevention and Analysis

Subject: Label and Labeling Review

Drug Name: Acuvail (Ketorolac Tromethamine Ophthalmic Solution); 0.45%

Application Type/Number: NDA# 22-427

Applicant: Allergan

OSE RCM #: 2008-1776-1
<table>
<thead>
<tr>
<th></th>
<th>CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>INTRODUCTION</td>
</tr>
<tr>
<td>2</td>
<td>METHODS AND MATERIALS</td>
</tr>
<tr>
<td>3</td>
<td>RECOMMENDATIONS</td>
</tr>
<tr>
<td>3.1</td>
<td>Comments to the Applicant</td>
</tr>
</tbody>
</table>
1 INTRODUCTION
This review was written in response to a request from the Division of Anti-Infective and Ophthalmologic Products to evaluate the container labels, foil labeling, and carton labeling for the product Acuvail (NDA 22-427), for areas that could lead to medication errors.

2 METHODS AND MATERIALS
The Division of Medication Error Prevention and Analysis (DMEPA) used principles of Human Factors and Failure Mode and Effects Analysis (FMEA) in our evaluation of the container labels and carton labeling submitted as part of the July 17, 2009 submission (see Appendices A through D).

3 RECOMMENDATIONS
Our evaluation noted areas where information on the container labels, foil labeling and carton labeling can be improved to minimize the potential for medication errors. DMEPA does not have any comments on the insert labeling. Section 2.1 Comments to the Applicant contains our recommendations for the container label, foil labeling, and carton labeling. We request the recommendations in Section 2.1 be communicated to the Applicant prior to approval.

Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have further questions or need clarifications on this review, please contact Darrell Jenkins, Project Manager, at 301-796-0558.

3.1 COMMENTS TO THE APPLICANT

A. General Comments on Foil Labeling and Carton Labeling
   1. Increase the size of the product strength by using color, boxing or some other means in order to improve its prominence.
   2. Include a route of administration on the principle display panel in accordance with 21 CFR 201.100 (b)(3).

B. Container Labels (LDPE vial)
   1. From the schematic provided, the imprint of the lot and expiration date will appear directly behind the strength of the product. Imprinting LDPE’s on both sides blurs the lettering. Since the strength is the differentiating factor between this product and your other ketorolac ophthalmic solutions, we request you relocate the lot and expiration date so that it does not overlap with any text on the principle display panel of the LDPE.
   2. Include the proprietary name above the established name in accordance with 21 CFR 201.10 (g)(1).

C. Foil Labeling
   Include the proprietary name above the established name on the foil labeling. Please ensure that the presentation is in accordance with 21 CFR 201.10 (g)(2).
D. Carton Labeling

1. The teardrop shaped graphic that appears to the right of the proprietary name is more prominent than the proprietary name, established name and product strength. Decrease the prominence of the teardrop graphic or relocate the teardrop graphic away from the proprietary name, established name and product strength.

2. Consider changing the blue and white color scheme of the carton to avoid confirmation bias in product selection between Acuvail and Acular. Acular uses a similar blue and white color scheme. If Acuvail is shelved alphabetically is placed side-by-side with other Allergan ophthalmic products (i.e., Acular), confirmation bias may lead practitioners to select the wrong product.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/  
Felicia Duffy  
7/21/2009 03:38:46 PM  
DRUG SAFETY OFFICE REVIEWER

Kellie Taylor  
7/21/2009 04:31:19 PM  
DRUG SAFETY OFFICE REVIEWER

Denise Toyer  
7/21/2009 04:52:43 PM  
DRUG SAFETY OFFICE REVIEWER

Carol Holquist  
7/21/2009 04:54:18 PM  
DRUG SAFETY OFFICE REVIEWER
Memorandum

***Pre-Decisional Agency Information***

Date:       June 30, 2009

To:         Raphael Rodriguez
            Regulatory Health Project Manager
            Division of Anti-Infective and Ophthalmology Products

From:       Beth Carr, Pharm.D., Regulatory Review Officer
            Lynn Panholzer, Pharm.D., Regulatory Review Officer
            Division of Drug Marketing, Advertising, and Communications
            (DDMAC)

Subject:    Acuvail™ (ketorolac tromethamine ophthalmic solution) 0.45%
            NDA: 22-427

DDMAC has reviewed the proposed product labeling, including the package insert (PI), draft carton label, draft container vial, and the draft container pouch for Acuvail™ (ketorolac tromethamine ophthalmic solution) 0.45% (Acuvail) submitted by the applicant on September 29, 2008; and we offer the following comments. We have also taken into consideration the labeling for Acular LS (ketorolac tromethamine ophthalmic solution), Xibrom (bromfenac sodium ophthalmic solution), and Nevanac (nepafenac ophthalmic suspension). Please feel free to contact me at (301) 796-3674 with any questions or clarifications.

Package Insert

GENERAL

Please consider abbreviating "nonsteroidal anti-inflammatory drug" to NSAID throughout PI after its first definition.

(b) (4)
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\/_s_/  

Beth M Carr  
7/9/2009 09:02:39 AM  
DDMAC PROFESSIONAL REVIEWER