CLINICAL REVIEW

Application Type  Supplemental NDA 006
Submission Number  205388
Submission Code  SDN-170

Letter Date  6/9/17
Stamp Date  6/9/17
PDUFA Goal Date  12/9/17

Reviewer Name  William M. Boyd, MD
Review Completion Date  11/17/17

Established Name  phenylephrine/ketorolac intraocular solution
(Proposed) Trade Name  Omidria
Therapeutic Class  sympathomimetic/NSAID
Applicant  Omeros

Priority Designation  P

Dosage Form  intraocular solution
Dosing Regimen  for use in an ocular irrigating solution

Proposed Indications  For the prevention of intraoperative miosis, and reduction of postoperative ocular pain

Intended Population  Patients undergoing cataract surgery
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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

NDA 205388/S-006 is recommended for approval with the revised labeling identified in this review. The clinical studies contained in this submission support the use of Omidria for the prevention of intraoperative miosis and reduction of post-operative pain in the pediatric population from neonates to adolescents (birth to younger than 17 years).

1.2 Risk Benefit Assessment

The benefits of using this drug product outweigh the risks for the above indication.

1.3 Recommendations for Post-Marketing Risk Management Activities

There are no proposed risk management actions except the usual post-marketing collection and reporting of adverse experiences associated with the use of drug product.

1.4 Recommendations for other Post Marketing Study Commitments

There are no recommended Phase 4 clinical study commitments.

2 Introduction and Regulatory Background

2.1 Product Information

Omidria (i.e., OMS302) is a fixed-dose combination product containing phenylephrine hydrochloride (PE), an $\alpha_1$-adrenergic receptor agonist, and the NSAID ketorolac tromethamine (KE), a non-selective cyclooxygenase (COX) COX-1/COX-2 inhibitor. Omidria is added to standard irrigation solution used during cataract surgery.

NDA 205388 Omidria (phenylephrine and ketorolac intraocular solution) 1% / 0.3% was approved on May 30, 2014.

The purpose of this efficacy supplement is to label Omidria for use in pediatric patients. Pediatric clinical study report OMS302-ILR-007 was designed to provide clinical support for the newly proposed labeling. Reference is made to the Written Request that was received from the Agency on October 3, 2013. Study OMS302-ILR-007 was submitted by the applicant to satisfy the NDA postmarketing study requirement 2167-1 and respond to the Written Request.
2.2 Tables of Currently Available Treatments for Proposed Indications

None, for both indications concurrently. There are several NSAIDs approved for topical use, pre-operatively for prevention of miosis and post-operatively for pain.

2.3 Availability of Proposed Active Ingredient in the United States

NDA 11663: Cyclomydril (cyclopentolate hydrochloride and phenylephrine hydrochloride) Ophthalmic Solution (withdrawn FR Effective 04/30/1984).

ANDA 84300: Cyclopentolate hydrochloride and phenylephrine hydrochloride ophthalmic solution. Indicated for the production of mydriasis: Combination of an adrenergic agent (which activates iris dilator muscle) and an anticholinergic agent (which paralyzes the iris sphincter muscle and accommodative muscle of the ciliary body).

NDA 000607: Isophrin (phenylephrine hydrochloride) Ophthalmic Solution (withdrawn FR effective 03/02/1994).

NDA 19700: Acular

ANDA 75222: Ketorolac injection

2.4 Important Safety Issues with Consideration to Related Drugs

The predominant actions of PE are on the cardiovascular system, where it produces significant vasoconstriction, but lacks chronotropic actions on the heart. Systemic side effects have been reported following topical ophthalmic instillation of PE. Uncommon systemic adverse reactions include elevated blood pressure, stroke, rupture of aneurysms, tachycardia, ventricular arrhythmia, myocardial infarction, and subarachnoid hemorrhage. Coronary artery spasm and pulmonary embolism in diabetics and acute pulmonary edema in premature infants have also been reported. The risk of these systemic side effects appears to be related to the PE concentration, i.e., 10% PE is associated with a higher risk than 2.5% PE. Patients taking certain systemic medications are more sensitive to the pressor effects of PE; therefore PE should be used with caution in patients on MAO inhibitors.

Ketorolac inhibits COX-1 and COX-2. Systemic adverse reactions are rare following topical ophthalmic instillation of KE. Reports have included exacerbation of asthma due to systemic absorption, gastrointestinal irritation and ulceration, inhibition of platelet function and increased bleeding, and renal disease. Idiosyncratic drug reactions may also occur. The most common adverse reactions are local in nature, such as transient burning, stinging, and conjunctival hyperemia. More serious but less common local reactions include corneal complications such as SPK, epithelial defects, corneal melting, and delayed wound healing and re-epithelialization.
Post-marketing experience with topical NSAIDs suggests that patients with complicated ocular surgical procedures, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases, rheumatoid arthritis, or repeat ocular surgical procedures within a short period may be at an increased risk for corneal adverse events.

### 2.5 Summary of Pre-submission Regulatory Activity Related to Submission

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<th>Event Description</th>
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<tr>
<td>IND 78227 Agreed Pediatric Study Plan Acknowledgment Letter</td>
<td>9/13/13</td>
</tr>
<tr>
<td>IND 78227 Written Request</td>
<td>10/3/13</td>
</tr>
<tr>
<td>NDA 205388 Approval</td>
<td>5/30/14</td>
</tr>
</tbody>
</table>

### 2.6 Other Relevant Background Information

None.

### 3 Ethics and Good Clinical Practices

#### 3.1 Submission Quality and Integrity

DSI was consulted for this study. There were no issues preliminarily identified to indicate a problem with submission integrity or quality.

#### 3.2 Compliance with Good Clinical Practices

There is no evidence to suggest that the clinical trials were not conducted in compliance with good clinical practices.

#### 3.3 Financial Disclosures

See Appendix 9.3 for Financial Disclosures template.

### 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

#### 4.1 Chemistry Manufacturing and Controls

There is no new Chemistry Manufacturing and Controls information submitted in this supplemental application.

Omidria is a preservative-free, bisulfite-free, clear, colorless, sodium citrate-buffered, sterile solution concentrate containing 12.4 mg/mL of phenylephrine hydrochloride and 4.24 mg/mL...
ketorolac tromethamine in a single-use vial. For administration, OMS302 must be diluted prior to use; 4.0 mL of OMS302 drug product is diluted in 500 mL of standard irrigation solution (ie. balanced salt solution), resulting in a solution with PE at a final concentration of approximately 480 $\mu$M (0.0098% w/v) and KE at a final concentration of approximately 89 $\mu$M (0.0034% w/v).

4.2 Clinical Microbiology

There is no clinical microbiology review for this product. It is not an anti-infective.

4.3 Pre-clinical Pharmacology/Toxicology

There is no new Pharmacology/Toxicology information submitted in this supplemental application.

The drug substances in Omidria have been used individually for many years. Phenylephrine, a $\alpha_1$-adrenergic receptor agonist, was initially introduced into clinical use at least 75 years ago and KE (Toradol), an NSAID, was first approved by the United States FDA in 1989. Omidria is the first drug product containing both agents.

See original Pharm/Tox review dated 4/21/14 in DARRTS for additional information.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Phenylephrine is an $\alpha_1$-adrenergic receptor agonist. Ketorolac is a NSAID that inhibits both COX-1 and COX-2.

4.4.2 Pharmacodynamics

There is no new Clinical Pharmacology information submitted in this supplemental application. See original Clinical Pharmacology review dated 4/22/14 in DARRTS for additional information.
4.4.3 Pharmacokinetics

There is no new Clinical Pharmacology information submitted in this supplemental application. See original Clinical Pharmacology review dated 4/22/14 in DARRTS for additional information.

5 Sources of Clinical Data

5.1 Tables of Clinical Studies

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Study Identifier</th>
<th>Study Design and Type of Control</th>
<th>Test Product(s); Dosage Regimen; Route of Administration</th>
<th>Number of Subjects</th>
<th>Healthy Subjects or Diagnosis of Patients</th>
<th>Duration of Tx</th>
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<tr>
<td>Phase 3</td>
<td>OMS302- ILR-007</td>
<td>Randomized, parallel group, double-masked, active-controlled study</td>
<td>OMS302 (µM PE and µM KE) or PE alone (µM) diluted in balanced salt solution (BSS); Single dose, intraocular irrigation and intracameral perfusion</td>
<td>78 (37 OMS302, 41 PE)</td>
<td>Pediatric subjects (0 to 3 years) undergoing cataract extraction with or without lens replacement</td>
<td>Single Dose</td>
</tr>
</tbody>
</table>

5.2 Review Strategy

The sources of clinical data utilized in this review include the studies listed in section 5.1.

5.3 Discussion of Individual Studies

Study OMS302- ILR-007

DESIGN
This study was a randomized, parallel-group, double-masked, phenylephrine-controlled study of OMS302 in young children ages birth through three years undergoing unilateral cataract extraction. Administration of test irrigation solutions took place in a double-masked fashion. Subjects were randomized 1:1 to OMS302 or phenylephrine. Randomization to treatment group was stratified within site according to whether an intraocular lens (IOL) would be implanted during the surgical procedure.
Intraoperative pupil size was determined by measurement of pupil diameter from still photos captured from video recordings of the procedure. Pupil diameter measurements was performed immediately prior to the initial incision and at one-minute intervals until the end of the procedure (wound closure). Pain was assessed by the Alder Hey Triage Pain Score. Safety and tolerability was assessed based on adverse events, intraocular pressure, best corrected distance visual acuity, and vital signs for 90 days postoperatively.

Study procedures was performed at screening, at baseline prior to surgery, intraoperatively, and postoperatively at approximately 3 hours, 6 hours, 9 hours, 24 hours (Day 2), 7 days (Day 8), 21-28 days (Day 22-29), and day 90. The length of time for subject participation was approximately 13 to 17 weeks: up to 28 days in the screening process and 90 days in the postoperative period.

NUMBER OF SUBJECTS (PLANNED)
A total of approximately 60 subjects (at least 30 subjects per arm) were to be enrolled and treated in this study.

OBJECTIVE(S)
The co-primary objectives of this study were to evaluate the effect of OMS302 compared to phenylephrine when administered in irrigation solution during cataract extraction with or without lens replacement (cataract extraction) on:

- Intraoperative pupil diameter,
- Acute postoperative pain, and
- Safety as measured by adverse events.

STUDY ENDPOINTS
Study endpoints were:

- Change in pupil diameter over time from surgical baseline (immediately prior to surgical incision) to the end of the surgical procedure (wound closure).
- Acute postoperative pain measured by the Alder Hey Triage Pain Score at six hours postoperatively. The Alder Hey Triage Pain Score will be assessed at approximately 3 hours, 6 hours, 9 hours, and 24 hours following the end of the surgical procedure
- Safety as assessed by the incidence of adverse events (AE), including infections, serious adverse events (SAE), postoperative intraocular pressure, postoperative best corrected distance visual acuity and vital signs.

I. Pupil Diameter During Surgery
Change in pupil diameter over time from surgical baseline (immediately prior to surgical incision) to the end of the surgical procedure (wound closure) will be summarized using descriptive statistics by treatment group and time point (every minute).

The mean change in pupil diameter during surgery will be calculated as the area-under-the curve (AUC) divided by the surgery time minus the baseline for each subject. Summary
statistics of the mean AUC of change from baseline will be provided by stratum and treatment group. A generalized Cochran-Mantel-Haenszel (CMH) test stratified by the randomization strata will be used to compare the two treatment groups.

II. Acute Postoperative Pain
Postoperative pain will be measured by the Alder Hey Triage Pain Score at approximately 3, 6, 9, and 24 hours following the end of the surgical procedure. The mean scores by treatment group at the six-hour time point will be compared by a generalized Cochran-Mantel-Haenszel (CMH) test stratified by the randomization strata.

III. Safety Analyses
The safety data, including AEs, intraocular pressure, best-corrected distance visual acuity, vital signs, concomitant medications, and reasons for withdrawal from study will be descriptively summarized by treatment group. Adverse events will be coded according to preferred term and system/organ class using the Medical Dictionary for Regulatory Activities (MedDRA) adverse event coding dictionary.

INCLUSION CRITERIA
1. Are 0 to three years of age at the time of surgery.
2. Are to undergo unilateral primary cataract extraction.
3. Have informed consent and Health Insurance Portability and Accountability Act (HIPAA) Authorization provided by a parent or legal guardian in accordance with local regulations and governing IRB/IEC requirements.
4. Parent or legal guardian indicated that they understand and are able, willing, and likely to fully comply with study procedures and restrictions.

EXCLUSION CRITERIA
1. Corneal diameter less than nine millimeters in the study eye.
2. Hypersensitivity to phenylephrine, ketorolac, or other Non-Steroidal Anti-Inflammatory Drugs (NSAID), including aspirin, or latex.
3. Surgeon’s expectation that the protocol-specified mydriatic regimen will not be adequate to perform the procedure and that additional mydriatic treatment (pharmacological or mechanical) will be required.
4. Presence of clinically significant gastrointestinal, cardiovascular, hepatic, renal, hematological, endocrine, neurological, psychiatric, respiratory, or other medical condition that could increase the risk to the subject as determined by the Investigator.
5. Presence of active or suspected viral, bacterial, or fungal disease in the study eye.
6. Use of any topical medication in the study eye within seven days prior to surgery, except for medications needed to examine the eye or prepare for surgery.
7. Have a post-traumatic cataract.
8. History of uveitis or evidence of past uveitis such as synechiae or keratic precipitates in the study eye.
9. Have an ocular neoplasm in the study eye.
10. Have a clinically significant infection.
11. Have suspected permanent or low vision in the fellow non-study eye, unless caused by a cataract. The study eye must not be the subject’s only good eye.
12. Use of systemic corticosteroids or non-steroidal anti-inflammatory drugs in the seven days prior to surgery.
13. Have a history of clinically significant corticosteroid-induced intraocular pressure increase.
14. Use of any medication for ocular hypertension or glaucoma in the study eye.
15. Use of monoamine oxidase inhibitors for 21 days preoperatively.
17. Participating in any investigational drug or device trial within the 30 days prior to the day of surgery.
18. History of intraocular non-laser surgery in the study eye within the three months prior to the day of surgery, or intraocular laser surgery in the study eye within 30 days prior to the day of surgery.
19. Presence of any condition that the Investigator believes would put the subject at risk or confound the interpretation of the study data.
20. Be a member of the immediate family of the Investigator or employees of the investigative site. Immediate family is defined as the Investigator's or employees’ natural or legally adopted child.

INVESTIGATIONAL PRODUCT/REFERENCE PRODUCT

- OMS302 diluted in balanced salt solution (BSS/BSS Plus) and administered as irrigation solution during cataract extraction. OMS302 is the combination of \( \mu \text{M PE} \) and \( \mu \text{M KE} \).
- Phenylephrine \( \mu \text{M} \) diluted in BSS/BSS Plus and administered in standard irrigation solution during cataract extraction.

Reviewer’s Comments:

Study OMS302- ILR-007 was not powered to establish efficacy of Omidria in the pediatric population. Effective use of Omidria in this population is supported by evidence from adequate and well-controlled studies of Omidria in adults.
# PEDIATRIC CLINICAL STUDY OMS302-ILR-007

Site Number, Number of Randomized Patients, and List of Investigators

<table>
<thead>
<tr>
<th>Site No.</th>
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<th>Investigator Name and Address</th>
<th>Sub-Investigator(s) Name</th>
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<tr>
<td>240</td>
<td>12</td>
<td>David Plager, MD</td>
<td>Michele Whitaker</td>
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<tr>
<td></td>
<td></td>
<td>Riley Hospital for Children</td>
<td>Daniel Neely, MD</td>
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<tr>
<td></td>
<td></td>
<td>705 Riley Hospital Drive, Room 3340</td>
<td>Kathryn Haider, MD</td>
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<tr>
<td></td>
<td></td>
<td>Indianapolis, IN 46202</td>
<td>Heather Smith, MD</td>
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<td></td>
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<td></td>
<td>Janae Kegeris, RN</td>
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<td>Mallory Mack, COA</td>
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<tr>
<td>241</td>
<td>10</td>
<td>Scott Lambert, MD</td>
<td>Natalie Weil, MD</td>
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<tr>
<td></td>
<td></td>
<td>Phoebe Lenhart, MD (replaced Dr.</td>
<td>Jim Rhodes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lambert after he resigned)</td>
<td>Judy Brower</td>
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<tr>
<td></td>
<td></td>
<td>Emory University Eye Center</td>
<td>Phoebe Lenhart, MD</td>
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<td>1365 B Clifton Road, NE</td>
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<td>Atlanta, GA 30322</td>
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<td>M. Edward Wilson, MD</td>
<td>Rupal Trivedi, MD</td>
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<td>Medical University of South Carolina</td>
<td>Carol Bradham, COA</td>
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<td></td>
<td>Storm Eye Institute</td>
<td>James Fant, MBA</td>
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<td>167 Ashley Ave., Room 218</td>
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<td>244</td>
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<td>Erin Stahl, MD</td>
<td>Rebecca Dent, COA</td>
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<td>Children’s Mercy Clinics on</td>
<td>Lezlie Richardson-Bond, COA</td>
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<td></td>
<td></td>
<td>Broadway/Ophthalmology Department</td>
<td>Allison King, PharmD</td>
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<td></td>
<td></td>
<td>3101 Broadway Blvd.</td>
<td>Emily Broxterman, MD</td>
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<td></td>
<td>Kansas City, MO 64111</td>
<td>Justin Marsh</td>
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<td></td>
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<td>Amanda Drees, PharmD</td>
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<td>Kori Hess, PharmD</td>
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<tr>
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<td>Pamela Zacharko, Pharmacy Tech</td>
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<tr>
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<td></td>
<td>Matthew Recko, MD</td>
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<tr>
<td></td>
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<td>Denise Hug, MD</td>
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<tr>
<td></td>
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<td>Timothy Lindquist, MD</td>
</tr>
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### Site Number, Number of Randomized Patients, and List of Investigators (Continued)

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<th>Investigator Name and Address</th>
<th>Sub-Investigator(s) Name</th>
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</table>
| 245      | 5                 | Deborah VanderVeen, MD  
Children's Hospital Boston, Department of Ophthalmology, Fegan 4  
300 Longwood Avenue  
Boston, MA 02115 | Carolyn Wu, MD  
Jason Mantagos, MD  
Danielle Ledoux, MD  
Ankoor Shah, MD  
Rocco Anzaldi, PharmD |
| 246      | 4                 | Serena Wang, MD  
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Dallas, TX 75390-9057 | David Weakley, MD  
Ruth Merryman, PharmD  
Janie Burroughs  
Priscilla Diaz  
Jordan Whitehill, PharmD  
Emily Linsenbardt, COA  
Mike Molai, BS  
Bianca Larsen, MS  
Susan Forshaw, RN  
Nancy Hernandez  
Shahn Laymance, RN  
Vijayakumari Christopher, RN  
Diane Marie Ramoz  
Kathryn Richey, RN |
| 247      | 6                 | Bibiana Reiser, MD  
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4650 Sunset Blvd.  
Los Angeles, CA 90027 | Thomas Lee, MD  
Jonathan Kim, MD  
Maria Uribe, OD  
Victor Zendeljas  
Dilshad Contractor  
Julia Johnston |
| 248      | 0                 | Bahram Rahmani, MD  
Ann and Robert H. Lurie Children’s Hospital of Chicago  
225 E. Chicago Avenue, Box 70  
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Wanwan Xu, MD  
Kimberly McCarter, CPHT  
Jamie Sovcik, PharmD  
Hanta Ralay-Ranaivo, SC  
Mary Wright, CPHT  
Rebecca Mets-Halgrimson, MD |
| 249      | 0                 | John Roarty, MD  
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Elena Marie Gianfermi, MD  
Reecho Bahl, MD  
Angella Borski, RN |
| 250      | 3                 | Deborah VanderVeen, MD  
Children’s Hospital Boston at Waltham  
9 Hope Avenue  
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Jason Mantagos, MD  
Danielle Ledoux, MD  
Ankoor Shah, MD  
Rocco Anzaldi, PharmD |
| 251      | 7                 | David Morrison, MD  
Vanderbilt University Medical Center  
2311 Pierce Ave  
Nashville, TN 37232-8808 | Meghon Flemmons, MD  
Anvesh Reddy, MD |
<table>
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<td>2</td>
<td>Federico Velez, MD Stein Eye Institute, UCLA 100 Stein Plaza, 3-519 Los Angeles, CA 90095</td>
<td>Stacy Pinealess, MD Joseph Deme, MD Melinda Chang, MD Tina Damarjian, MD</td>
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<tr>
<td>253</td>
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<td>Kartik Kumar, MD Robert Cizik Eye Clinic 6400 Fannin Street, Suite 1800 Houston, TX 77030</td>
<td>Megan Geloneck, MD Laura Baker Ephrem Melese Theodore Baker</td>
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<tr>
<td>254</td>
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<td>Norman Medow, MD Montefiore Medical Center 332 Rochambeau Avenue Centennial Building, 3rd Floor Bronx, NY 10467</td>
<td>Ilana Friedman, MD Jose Rosado</td>
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<tr>
<td>255</td>
<td>2</td>
<td>Mary O’Hara, MD University of California – Davis Ophthalmology &amp; Vision Science 4860 Y Street, Suite 2400 Sacramento, CA 95817</td>
<td>Nandini Gandhi, MD Tania Hashmi, BMS</td>
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<tr>
<td>256</td>
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<td>Sharon Freedman, MD Duke Eye Center 2351 Erwin Road Durham, NC 27710</td>
<td>Sarah Jones</td>
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<td>257</td>
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<td>Michael Struck, MD University of Wisconsin – Madison Department of Ophthalmology &amp; Visual Sciences 2870 University Avenue, Suite 206 Madison, WI 53705</td>
<td>Yasmin Bradfield, MD Melanie Schmitt, MD Kristine Dietzman, CCRC</td>
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</tbody>
</table>
6 Review of Efficacy

Efficacy Summary

6.1 Indication

For the prevention of intraoperative miosis, and reduction of postoperative ocular pain

6.1.1 Methods

Use of Omidria in in the pediatric population from neonates to adolescents (birth to younger than 17 years) is supported by evidence from adequate and well-controlled studies of Omidria in adults with additional data from a single active-controlled safety study in pediatric patients up to 3 years of age (Study OMS302 ILR-007).
6.1.2 Demographics - Study OMS302- ILR-007

<table>
<thead>
<tr>
<th>Table 12</th>
<th>Subject Demographics (Full Analysis Set)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PE (N = 39)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>39</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1.4 (1.2)</td>
</tr>
<tr>
<td>Median</td>
<td>0.9</td>
</tr>
<tr>
<td>Min, Max</td>
<td>0.1, 3.6</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>20 (51%)</td>
</tr>
<tr>
<td>Female</td>
<td>19 (49%)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
</tr>
<tr>
<td>Hispanic or Latino</td>
<td>10 (26%)</td>
</tr>
<tr>
<td>Not Hispanic or Latino</td>
<td>29 (74%)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>American Indian or Alaska Native</td>
<td>0</td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
</tr>
<tr>
<td>Black or African American</td>
<td>3 (8%)</td>
</tr>
<tr>
<td>Native Hawaiian or Other Pacific Islander</td>
<td>0</td>
</tr>
<tr>
<td>White</td>
<td>30 (77%)</td>
</tr>
<tr>
<td>Other</td>
<td>6 (15%)</td>
</tr>
</tbody>
</table>

Source: Section 14.1, Table 23

Overall, ages ranged from 0.1 to 3.9 years with a mean (SD) of 1.2 (1.2) years. The majority of subjects were male (37 subjects [51%]), not Hispanic or Latino (62 subjects [86%]), and white (56 subjects [78%]). Subjects were treated with study drug at 13 study sites geographically located to reflect the ethnic and racial diversity of the general US population.

The PE group contained 10 subjects (26%) who were Hispanic or Latino. The remainder of the group were not Hispanic or Latino. In the OMS302 group, 33 subjects (100%) were not Hispanic or Latino. There were no other clinically meaningful differences between treatment groups in demographics or baseline characteristics.
6.1.3 Patient Disposition

A total of 83 subjects were consented and screened for this study; of these, 78 were randomized and 72 were treated at 13 study sites.

Five of the 83 subjects who consented were not randomized for the following reasons:
• Subject 241-011 did not satisfy all the inclusion and exclusion criteria.
• Subject 247-004 consented to the study but surgery was not scheduled prior to the end of the enrollment period.
• Subject 247-008 was unable to schedule a surgery date.
• Subject 248-001 could not commit to the study and withdrew consent prior to randomization.
• Subject 249-002 was withdrawn due to Investigator judgement regarding a medical condition.

Reviewer’s Comments:
Subject 249-002: withdrawn due to “Presence of medical condition that could increase the risk to the subject as determined by the principle investigator.” Condition is unspecified in the study report.
Six of the 78 subjects randomized in this study did not receive study treatment for the following reasons:

- Subjects 240-005 (PE) and 247-006 (OMS302) did not achieve adequate pupil dilation prior to surgery.
- Subject 241-012 (OMS302) had an AE (upper respiratory tract infection) which precluded surgery.
- Subject 247-001 (OMS302) withdrew consent after randomization.
- Subject 249-001 (OMS302) had an AE (influenza) which precluded surgery.
- Subject 255-001 (PE) was given non-protocol specified eye drops prior to surgery, and was withdrawn due to this protocol deviation.

These six subjects were excluded from the safety and efficacy analyses.

Subject 257-001 was randomized to OMS302, but received PE. All other treated subjects received the treatment to which they were randomized.

There were three subjects (two OMS302 and one PE) who were randomized, received study treatment, and completed their primary efficacy assessments, and then discontinued from the study before completing all follow-up assessments. All three of these subjects were lost to follow-up. See following table.

<table>
<thead>
<tr>
<th>Table 9</th>
<th>Subject Disposition (Randomized Subjects)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PE (N = 41) n (%)</td>
</tr>
<tr>
<td>Number of Subjects Randomized</td>
<td>41 (100%)</td>
</tr>
<tr>
<td>Number of Subjects That Received Study Treatment(^a)</td>
<td>39 (95.1%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reason for Study Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completed Study</td>
</tr>
<tr>
<td>Lost to Follow-Up</td>
</tr>
<tr>
<td>Other(^b)</td>
</tr>
</tbody>
</table>

\(^a\) “Number of Subjects That Received Study Treatment” row specified number of subjects randomized to a particular group who received either masked treatment. Subject 257-001 was randomized to OMS302, but received PE.

\(^b\) “Other” category is subjects who were randomized, but not treated.

Source: Section 14.1, Table 19
6.1.4 Analysis of Pupil Diameter and Postoperative Pain

Study OMS302-ILR-007 was not powered to establish efficacy of Omidria in the pediatric population. Effective use of Omidria in this population is supported by evidence from adequate and well-controlled studies of Omidria in adults.

**PUPIL DIAMETER**

Pupil diameter measurements were taken (1) starting with initial incision and at 1-minute intervals until wound closure and (2) at the end of cortical clean-up from the videos of subjects’ surgical procedures.

**Reviewer’s Comments:**

*Mydriasis was maintained throughout surgery in both the PE and the OMS302 treatment groups.*

<table>
<thead>
<tr>
<th>Table 13</th>
<th>Mean Area-under-the-Curve (AUC) Analysis of Change from Baseline in Pupil Diameter (mm) during Surgery (Full Analysis Set)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PE (N = 39)</td>
</tr>
<tr>
<td>Mean AUCa</td>
<td>32</td>
</tr>
<tr>
<td>n with video data</td>
<td>0.22 (0.601)</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>0.15</td>
</tr>
<tr>
<td>Median</td>
<td>-0.88, 2.36</td>
</tr>
<tr>
<td>Min, Max</td>
<td>0.5990</td>
</tr>
</tbody>
</table>

Source: Section 14.2, Table 30

**POSTOPERATIVE PAIN**

Postoperative ocular pain was measured by the Alder Hey Triage Pain Score at 3, 6, 9, and 24 hours after surgery.

**Reviewer’s Comments:**

*There was no statistically significant difference in ocular pain as measured by the Alder Hey Triage Pain Score between the two treatment groups.*
7 Review of Safety

Safety Summary
The safety and effectiveness of Omidria have been established in the pediatric population from neonates to adolescents (birth to younger than 17 years). Use of Omidria in this population is supported by evidence from adequate and well-controlled studies of Omidria in adults with additional data from a single active-controlled safety study in pediatric patients up to 3 years of age (Study OMS302-ILR-007).

7.1 Methods
The safety data, including AEs, intraocular pressure, best-corrected distance visual acuity, vital signs, concomitant medications, and reasons for withdrawal from study will be descriptively summarized by treatment group. Adverse events will be coded according to preferred term and system/organ class using the Medical Dictionary for Regulatory Activities (MedDRA) adverse event coding dictionary.
7.2 Major Safety Results

7.2.1 Deaths

No subject deaths occurred during this study.

7.2.2 Nonfatal Serious Adverse Events

See section 7.2.4.

7.2.3 Dropouts and/or Discontinuations

See section 6.1.3.

7.2.4 Significant Adverse Events

<table>
<thead>
<tr>
<th>Table 18</th>
<th>Severe Adverse Events (Safety Population)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred Term</td>
<td>PE (N = 40) n (%)</td>
</tr>
<tr>
<td>Any Severe Adverse Event</td>
<td>0</td>
</tr>
<tr>
<td>Bronchiolitis</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory Syncytial Virus Infection</td>
<td>0</td>
</tr>
<tr>
<td>Vesicoureteric Reflux</td>
<td>0</td>
</tr>
</tbody>
</table>

Source: Section 14.3.1, Table 40

There were no severe AEs reported in the PE treatment group. Three severe AEs were reported in three subjects in the OMS302 treatment group: bronchiolitis, respiratory syncytial virus infection, and vesicoureteric reflux. All three were considered not related to study drug.

Reviewer’s Comments:

_These adverse events do not appear related to study drug._
7.3 Supportive Safety Results

7.3.1 Common Adverse Events

Table 38: Subject Incidence of Treatment-emergent Adverse Events by Preferred Term in Descending Frequency (Safety Population)

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>PE (N=40) n(%)</th>
<th>OMS302 (N=32) n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Event</td>
<td>18 (45.0%)</td>
<td>15 (46.9%)</td>
</tr>
<tr>
<td>Anterior chamber opacity</td>
<td>2 (5.0%)</td>
<td>2 (6.3%)</td>
</tr>
<tr>
<td>Intraocular pressure increased</td>
<td>2 (5.0%)</td>
<td>2 (6.3%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>3 (7.5%)</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Conjunctival haemorrhage</td>
<td>3 (7.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Bronchiolitis</td>
<td>0</td>
<td>2 (6.3%)</td>
</tr>
<tr>
<td>Conjunctival hyperaemia</td>
<td>1 (2.5%)</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Immunisation reaction</td>
<td>2 (5.0%)</td>
<td>0</td>
</tr>
<tr>
<td>Acquired epiblepharon</td>
<td>1 (2.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Anisometropia</td>
<td>1 (2.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Anterior capsule contraction</td>
<td>1 (2.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Anterior chamber inflammation</td>
<td>0</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Bronchial hyperreactivity</td>
<td>1 (2.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>0</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Corneal abrasion</td>
<td>0</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Cough</td>
<td>0</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Dermatitis contact</td>
<td>1 (2.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Discomfot</td>
<td>0</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Dry eye</td>
<td>0</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Eczema</td>
<td>0</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Eustachian tube operation</td>
<td>1 (2.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Eye injury</td>
<td>0</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Eyelid pross</td>
<td>0</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Flushing</td>
<td>1 (2.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1 (2.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Iris adhesions</td>
<td>0</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Laceration</td>
<td>1 (2.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>1 (2.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Pain</td>
<td>1 (2.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Persistent papillary membrane</td>
<td>0</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Procedural pain</td>
<td>0</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Respiratory syncytial virus infection</td>
<td>0</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Retinal haemorrhage</td>
<td>0</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Toothache</td>
<td>1 (2.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>0</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Vesicoureteric reflux</td>
<td>0</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Vitreous fibrin</td>
<td>0</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Vitreous haemorrhage</td>
<td>1 (2.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>1 (3.1%)</td>
</tr>
<tr>
<td>Wheezing</td>
<td>1 (2.5%)</td>
<td>0</td>
</tr>
</tbody>
</table>

C:\Shares\SAPROG\sapprod\OMS302\ILR007\Tables\code\T_AE_PT.sas

Date: March 6, 2017 2:51 PM

Reference ID: 4190348
Reviewer’s Comment:
The most frequently observed AEs overall were anterior chamber opacity, an increase in IOP, pyrexia, conjunctival hemorrhage, bronchiolitis, and immunization reaction.

“Anterior chamber opacity” in the preceding table refers to retained anterior chamber triamcinolone acetate used for visualization. “immunization reaction” refers to elevated temperature post immunization.

There is no overall difference in safety was observed between pediatric and adult patients.

7.3.2 Laboratory Findings

Clinical laboratory assessments were neither planned nor performed during this study. Only baseline pregnancy tests.

7.4 Other Safety Explorations

Not applicable.

7.5 Additional Safety Explorations

7.5.1 Human Carcinogenicity

Because of the low expected absorption of LE in topical preparations, no carcinogenicity studies were conducted in the original application.

7.5.2 Human Reproduction and Pregnancy Data

This drug has not been tested in pregnant women.

7.5.3 Pediatrics and Effect on Growth

Efficacy for pediatric patients ages 3 years 1 month to 17 years was extrapolated from the birth to 3 year study and from the three completed adult studies for the same indication using the same formulation.

This application was placed on the schedule of the Pediatric Exclusivity Board for October 17, 2017. The Board granted exclusivity.
7.5.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Omidria is a non-narcotic and does not have abuse potential.

7.6 Additional Submissions

None.

8 Post-marketing Experience

Omidria (phenylephrine and ketorolac injection) 1% / 0.3% was approved in the United States (US) in May 2014 (NDA 205388). Postmarketing reporting requirements have been met with quarterly Periodic Adverse Drug Experience Reports (PADERs). The most recent PADER was submitted on March 30, 2017.

Periodic Safety Update Reports (PSURs) have been submitted to the European Medicines Agency (EMA) semi-annually since approval of Omidria July 25, 2015. The product is commercially available in the US only. Therefore, all postmarketing data reflects the US region only at this time. Since approval, there have been no significant new information that affects the safety, effectiveness, or labeling of Omidria.

9 Appendices

9.1 Literature Review/References

A comprehensive literature search did not reveal any new information on Omidria not included in this supplemental application.

9.2 Advisory Committee Meeting

No Advisory Committee Meeting was held. There were no new issues raised in the review of the application which were thought to benefit from an Advisory Committee Meeting.

9.3 Financial Disclosures

See following page.

9.4 Labeling Recommendations

See attached package insert. Acceptable.
Appendix - Financial Disclosure Template

Clinical Investigator Financial Disclosure Review Template

Application Number: 205388/S-006
Submission Date(s): 6/9/17
Applicant: Omeros
Product: phenylephrine/ketorolac
Reviewer: William M. Boyd, MD
Date of Review: 11/17/17
Covered Clinical Study (Name and/or Number): OMS302-ILR-007

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Was a list of clinical investigators provided?</td>
<td>☒</td>
<td></td>
<td>(Request list from applicant)</td>
</tr>
<tr>
<td>Total number of investigators identified:</td>
<td>17 sites</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of investigators who are sponsor employees (including both full-time and part-time employees):</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significant payments of other sorts:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proprietary interest in the product tested held by investigator:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Significant equity interest held by investigator in sponsor of covered study:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Is an attachment provided with details of the disclosable financial interests/arrangements:</td>
<td></td>
<td>(Request details from applicant)</td>
<td></td>
</tr>
<tr>
<td>Is a description of the steps taken to minimize potential bias provided:</td>
<td>☒</td>
<td>(Request information from applicant)</td>
<td></td>
</tr>
</tbody>
</table>
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0

<table>
<thead>
<tr>
<th>Is an attachment provided with the reason:</th>
<th>Yes □</th>
<th>No □ (Request explanation from applicant)</th>
</tr>
</thead>
</table>

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.1 Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

The disclosed financial interests/arrangements do not affect the approvability of the application.

This was a randomized, double-masked, parallel-group, phenylephrine-controlled study of the effect of Omidria added to standard irrigation solution on intraoperative pupil diameter and acute postoperative pain in children ages birth through three years undergoing unilateral cataract extraction with or without lens replacement.

In this study PE is the chloride salt, labeled as OMS302 PE HCl, and was manufactured specifically to permit study masking.

1 See [web address].
**INDICATIONS AND USAGE**

OMIDRIA is an alpha 1-adrenergic receptor agonist and nonselective cyclooxygenase inhibitor indicated for:
- Maintaining pupil size by preventing intraoperative miosis (1)
- Reducing postoperative pain (1)

OMIDRIA is added to an ocular irrigating solution used during cataract surgery or intraocular lens replacement.

**DOSAGE AND ADMINISTRATION**

- Each vial of OMIDRIA must be diluted prior to use for administration to a single patient undergoing cataract surgery or intraocular lens replacement.
- Dilute 4 mL of OMIDRIA in 500 mL of ocular irrigating solution. Irrigation solution is to be used as needed for the surgical procedure. (2)

**CONTRAINDICATIONS**

None. (4)

**WARNINGS AND PRECAUTIONS**

Systemic exposure to phenylephrine may cause elevations in blood pressure. (5.1)

**ADVERSE REACTIONS**

The most common reported adverse reactions (≥2%) are eye irritation, posterior capsule opacification, increased intraocular pressure, and anterior chamber inflammation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Omeros Corporation at 1-844-OMEROS1 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION

Revised: XXXX/2017
FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Omidria® is added to an ocular irrigating solution used during cataract surgery or intraocular lens replacement and is indicated for maintaining pupil size by preventing intraoperative miosis and reducing postoperative ocular pain.

2 DOSAGE AND ADMINISTRATION

Omidria must be diluted prior to intraocular use. For administration to patients undergoing cataract surgery or intraocular lens replacement, 4 mL of Omidria is diluted in 500 mL of ocular irrigating solution. Irrigation solution is to be used as needed for the surgical procedure for a single patient.

The storage period for the diluted product is not more than 4 hours at room temperature or 24 hours under refrigerated conditions.

Do not use if the solution is cloudy or if it contains particulate matter.

3 DOSAGE FORMS AND STRENGTHS

Omidria is an intraocular solution containing 10.16 mg/mL (1% w/v) of phenylephrine and 2.88 mg/mL (0.3% w/v) of ketorolac for use in a single patient.

4 CONTRAINDICATIONS

Omidria is contraindicated in patients with a known hypersensitivity to any of its ingredients.

5 WARNINGS AND PRECAUTIONS

5.1 Elevated Blood Pressure

Systemic exposure to phenylephrine can cause elevations in blood pressure.

5.2 Cross-Sensitivity or Hypersensitivity

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other non-steroidal anti-inflammatory drugs (NSAIDs). There have been reports of bronchospasm or exacerbation of asthma associated with the use of ketorolac in patients who either have a known hypersensitivity to aspirin/NSAIDs or a past medical history of asthma. Therefore, use Omidria with caution in individuals who have previously exhibited sensitivities to these drugs.
6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to the rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Table 1 shows frequently reported ocular adverse reactions with an incidence of \( \geq 2\% \) of adult patients as seen in the combined clinical trial results from three randomized, placebo-controlled studies [see Clinical Trials (14)].

### Table 1: Ocular Adverse Reactions Reported by \( \geq 2\% \) of Adult Patients

<table>
<thead>
<tr>
<th>MedDRA Preferred Term</th>
<th>Placebo (N=462)</th>
<th>Omidria (N=459)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular Events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anterior Chamber Inflammation</td>
<td>102 (22%)</td>
<td>111 (24%)</td>
</tr>
<tr>
<td>Intraocular Pressure Increased</td>
<td>15 (3%)</td>
<td>20 (4%)</td>
</tr>
<tr>
<td>Posterior Capsule Opacification</td>
<td>16 (4%)</td>
<td>18 (4%)</td>
</tr>
<tr>
<td>Eye Irritation</td>
<td>6 (1%)</td>
<td>9 (2%)</td>
</tr>
<tr>
<td>Foreign Body Sensation in Eyes</td>
<td>11 (2%)</td>
<td>8 (2%)</td>
</tr>
</tbody>
</table>

In a safety study that enrolled 72 pediatric patients up to 3 years old, no overall difference in safety was observed between pediatric and adult patients.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available data on Omidria use in pregnant women or animals to inform any drug-associated risks. Oral administration of ketorolac to rats during late gestation produced dystocia and increased pup mortality at a dose 740-times the plasma exposure at the recommended human ophthalmic dose [RHOD]. Since human systemic exposure to Omidria following a lens replacement procedure is low [see Clinical Pharmacology (12.3)], the applicability of animal findings to the risk of Omidria in humans during pregnancy is unclear. Omidria should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Premature closure of the ductus arteriosus in the fetus has occurred with third trimester use of oral and injectable NSAIDs. Ketonolac plasma concentrations are detectable following ocular Omidria administration [see Clinical Pharmacology (12.3)]. The use of Omidria during late pregnancy should be avoided.

Data

Animal Data
No well-controlled animal reproduction studies have been conducted with Omidria or phenylephrine.

Ketorolac, administered during organogenesis, did not cause embryofetal abnormalities or mortalities in rabbits or rats at oral doses of 3.6 mg/kg/day and 10 mg/kg/day, respectively. These doses produced systemic exposure that is 1150 times and 4960 times the plasma exposure (based on $C_{\text{max}}$) at the RHOD, respectively. When administered to rats during late gestation (after Day 17 of gestation) at oral doses up to 1.5 mg/kg/day (740 times the plasma exposure at the RHOD), ketorolac produced dystocia and increased pup mortality.

### 8.2 Lactation

**Risk Summary**

There are no data on the presence of Omidria in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to Omidria, following a lens replacement procedure is low [see Clinical Pharmacology (12.3)]. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for Omidria and any potential adverse effects on the breastfed child from Omidria.

### 8.4 Pediatric Use

The safety and effectiveness of Omidria have been established in the pediatric population from neonates to adolescents (birth to younger than 17 years). Use of Omidria in this population is supported by evidence from adequate and well-controlled studies of Omidria in adults with additional data from a single active-controlled safety study in pediatric patients up to 3 years old [see Clinical Studies (14)].

No overall differences in safety was observed between pediatric and adult patients.

### 8.5 Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and adult patients.

### 10 OVERDOSAGE

Systemic overdosage of phenylephrine may cause a rise in blood pressure. It may also cause headache, anxiety, nausea, vomiting, and ventricular arrhythmias. Supportive care is recommended.

### 11 DESCRIPTION

Omidria is a sterile aqueous solution, containing the $\alpha_1$-adrenergic receptor agonist phenylephrine HCl and the nonsteroidal anti-inflammatory ketorolac tromethamine, for addition to ocular irrigating solution.

The descriptions and structural formulae are:

**Phenylephrine Hydrochloride Drug Substance:**

- **Common Name:** phenylephrine hydrochloride
- **Chemical Name:** (-)-$m$-Hydroxy-$\alpha$-[(methylamino)methyl]benzyl alcohol hydrochloride
Figure 1: Chemical Structure for Phenylephrine HCl

Ketorolac Tromethamine Drug Substance:

Common Name: ketorolac tromethamine
Chemical Name: (±)-5-Benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid : 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1)
Molecular Formula: C₁₃H₁₃NO₃ · C₄H₁₁NO₃
Molecular Weight: 376.40 g/mole

Figure 2: Chemical Structure for Ketorolac Tromethamine

Omidria is a clear, colorless to slightly yellow, sterile solution concentrate with a pH of approximately 6.3.

Each vial of Omidria contains:

Actives: phenylephrine hydrochloride 12.4 mg/mL equivalent to 10.16 mg/mL of phenylephrine and ketorolac tromethamine 4.24 mg/mL equivalent to 2.88 mg/mL of ketorolac.

Inactives: citric acid monohydrate; sodium citrate dihydrate; water for injection; may include sodium hydroxide and/or hydrochloric acid for pH adjustment.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The two active pharmaceutical ingredients (API) in Omidria, phenylephrine and ketorolac, act to maintain pupil size by preventing intraoperative miosis, and reducing postoperative pain.

Phenylephrine is an α₁-adrenergic receptor agonist and, in the eye, acts as a mydriatic agent by contracting the radial muscle of the iris. Ketorolac is a nonsteroidal anti-inflammatory that inhibits both cyclooxygenase enzymes (COX-1 and COX-2), resulting in a decrease in tissue concentrations of prostaglandins to reduce pain.

Reference ID: 4190348
due to surgical trauma. Ketorolac, by inhibiting prostaglandin synthesis secondary to ocular surgical insult or direct mechanical stimulation of the iris, also prevents surgically induced miosis.

12.3 Pharmacokinetics

In a pharmacokinetic study evaluating Omidria, systemic exposure to both phenylephrine and ketorolac was low or undetectable.

A single-dose of Omidria as part of the irrigation solution was administered in 14 patients during lens replacement surgery. The volume of irrigation solution used during surgery ranged between 150 mL to 300 mL (median 212.5 mL). Detectable phenylephrine plasma concentrations were observed in one of 14 patients (range 1.2 to 1.4 ng/mL) during the first 2 hours after the initiation of Omidria administration. The observed phenylephrine plasma concentrations could not be distinguished from the preoperative administration of phenylephrine 2.5% ophthalmic solution prior to exposure to Omidria.

Ketorolac plasma concentrations were detected in 10 of 14 patients (range 1.0 to 4.2 ng/mL) during the first 8 hours after the initiation of Omidria administration. The maximum ketorolac concentration was 15 ng/mL at 24 hours after the initiation of Omidria administration, which may have been due to application of postoperative ketorolac ophthalmic solution.

14 CLINICAL STUDIES

Studies in Adults

The efficacy and safety of Omidria were evaluated in two Phase 3, randomized, multicenter, double-masked, placebo-controlled clinical trials in 808 adult patients undergoing cataract surgery or intraocular lens replacement.

Patients were randomized to either Omidria or placebo. Patients were treated with preoperative topical mydriatic and anesthetic agents. Pupil diameter was measured throughout the surgical procedure. Postoperative pain was evaluated by self-administered 0-100 mm visual analog scales (VAS).

Mydriasis was maintained in the Omidria-treated groups while the placebo-treated groups experienced progressive constriction.
At the end of cortical clean-up, 23% of placebo-treated patients and 4% of Omidria-treated patients had a pupil diameter less than 6 mm (p < 0.01).

Pain during the initial 10-12 hours postoperatively was statistically significantly less in the Omidria-treated groups than in the placebo-treated groups.
Figure 4: Postoperative Mean Visual Analog Scale (VAS) Scores for Pain

During the 10-12 hours postoperatively, 26% of Omidria-treated patients reported no pain (VAS = 0 at all timepoints) while 17% of placebo-treated patients reported no pain (p < 0.01).

**Study in Pediatric Patients**

The safety of Omidria was evaluated in a single, randomized, multicenter, double-masked, active-controlled clinical study in 72 pediatric patients up to 3 years old undergoing cataract surgery with or without intraocular lens replacement.
Patients were randomized to either Omidria or phenylephrine. Patients were treated with preoperative topical mydriatic and anesthetic agents. As in the adult studies, mydriasis was maintained in the Omidria-treated group. No overall differences in safety were observed between pediatric and adult patients.

16 HOW SUPPLIED/STORAGE AND HANDLING

Omidria (phenylephrine and ketorolac intraocular solution) 1%/0.3% is supplied in a clear, 5-mL glass, single-patient-use vial containing 4 mL of sterile solution, for addition to ocular irrigating solution.

Omidria is supplied in a multi-pack containing:

4 vials: NDC 62225-600-04 or
10 vials: NDC 62225-600-10

Storage: Store at 20° to 25°C (68° to 77°F). Protect from light.

17 PATIENT COUNSELING INFORMATION

Inform patients that they may experience sensitivity to light.

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Draft revised vial label is acceptable.
Draft revised carton label is acceptable.
This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM M BOYD
12/05/2017

WILEY A CHAMBERS
12/05/2017