

## CLINICAL REVIEW

Application Type Supplemental NDA 006  
Submission Number 205388  
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Reviewer Name William M. Boyd, MD  
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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 (b) (4), prevention of intraoperative miosis, and reduction of (b) (4) 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 <sup>(b) (4)</sup> 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**

IND 78227 Agreed Pediatric Study Plan Acknowledgment Letter	9/13/13
IND 78227 Written Request	10/3/13
NDA 205388 Approval	5/30/14

## **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

Type of Study	Study Identifier	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Tx
Phase 3	OMS302- ILR-007	Randomized, parallel group, double-masked, active-controlled study	OMS302 ((b)(4) μM PE and (b)(4) μM KE) or PE alone ((b)(4) μM) diluted in balanced salt solution (BSS); Single dose, intraocular irrigation and intracamerular perfusion	78 (37 OMS302, 41 PE)	Pediatric subjects (0 to 3 years) undergoing cataract extraction with or without lens replacement	Single Dose

### 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.
16. Prior participation in a clinical study of OMS302.
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 (b) (4)  $\mu\text{M}$  PE and (b) (4)  $\mu\text{M}$  KE.
- Phenylephrine ((b) (4)  $\mu\text{M}$ ) 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.*

Clinical Review  
 William M. Boyd, MD  
 NDA 205388/S-006  
 OMIDRIA (phenylephrine and ketorolac intraocular solution) 1% / 0.3%

**PEDIATRIC CLINICAL STUDY OMS302-ILR-007**

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

<b>Site No.</b>	<b>Number Randomized</b>	<b>Investigator Name and Address</b>	<b>Sub-Investigator(s) Name</b>
240	12	David Plager, MD Riley Hospital for Children 705 Riley Hospital Drive, Room 3340 Indianapolis, IN 46202	Michele Whitaker Daniel Neely, MD Kathryn Haider, MD Heather Smith, MD Janae Kegeris, RN Mallory Mack, COA
241	10	Scott Lambert, MD Phoebe Lenhart, MD (replaced Dr. Lambert after he resigned) Emory University Eye Center 1365 B Clifton Road, NE Atlanta, GA 30322	Natalie Weil, MD Jim Rhodes Judy Brower Phoebe Lenhart, MD
242	14	M. Edward Wilson, MD Medical University of South Carolina Storm Eye Institute 167 Ashley Ave., Room 218 Charleston, SC 29425	Rupal Trivedi, MD Carol Bradham, COA James Fant, MBA
244	6	Erin Stahl, MD Children's Mercy Clinics on Broadway/Ophthalmology Department 3101 Broadway Blvd. Kansas City, MO 64111	Rebecca Dent, COA Lezlie Richardson-Bond, COA Allison King, PharmD Emily Broxterman, MD Justin Marsh Amanda Drees, PharmD Kori Hess, PharmD Pamela Zacharko, Pharmacy Tech Matthew Recko, MD Denise Hug, MD Timothy Lindquist, MD

**Site Number, Number of Randomized Patients, and List of Investigators (Continued)**

Site No.	Number Randomized	Investigator Name and Address	Sub-Investigator(s) Name
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 University of Texas Southwestern Medical Center at Dallas 5323 Harry Hines Blvd. 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 Children's Hospital of Los Angeles 4650 Sunset Blvd. Los Angeles, CA 90027	Thomas Lee, MD Jonathan Kim, MD Maria Uribe, OD Victor Zendejas 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 Chicago, IL 60611	Sudhi Kurup, MD 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 Children's Hospital of Michigan, 3rd Floor CRC 3901 Beaubien Blvd. Detroit, MI 48201	May Faraon, PharmD Elena Marie Gianfermi, MD Reecha Bahl, MD Angella Borski, RN
250	3	Deborah VanderVeen, MD Children's Hospital Boston at Waltham 9 Hope Avenue Waltham, MA 02453	Carolyn Wu, MD 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

**Site Number, Number of Randomized Patients, and List of Investigators (Continued)**

<b>Site No.</b>	<b>Number Randomized</b>	<b>Investigator Name and Address</b>	<b>Sub-Investigator(s) Name</b>
252	2	Federico Velez, MD Stein Eye Institute, UCLA 100 Stein Plaza, 3-519 Los Angeles, CA 90095	Stacy Pineles, MD Joseph Demer, MD Melinda Chang, MD Tina Damarjian, MD
253	2	Kartik Kumar, MD Robert Cizik Eye Clinic 6400 Fannin Street, Suite 1800 Houston, TX 77030	Megan Geloneck, MD Laura Baker Ephrem Melese Theodore Baker
254	0	Norman Medow, MD Montefiore Medical Center 332 Rochambeau Avenue Centennial Building, 3rd Floor Bronx, NY 10467	Ilana Friedman, MD Jose Rosado
255	2	Mary O'Hara, MD University of California – Davis Ophthalmology & Vision Science 4860 Y Street, Suite 2400 Sacramento, CA 95817	Nandini Gandhi, MD Tania Hashmi, BMS
256	0	Sharon Freedman, MD Duke Eye Center 2351 Erwin Road Durham, NC 27710	Sarah Jones
257	3	Michael Struck, MD University of Wisconsin – Madison Department of Ophthalmology & Visual Sciences 2870 University Avenue, Suite 206 Madison, WI 53705	Yasmin Bradfield, MD Melanie Schmitt, MD Kristine Dietzman, CCRC

### 19.1. Study Schedule of Events

OMS302-ILR-007 Schedule of Events	Day -28 to -1	Day 1			Day 2	Day 8 <sup>1</sup>	Day 22-29 <sup>1</sup>	Day 90 <sup>1</sup> or Early Termination
	Screening	Baseline	Surgery	Post Surgery 3, 6 and 9 hours <sup>1</sup>	Post Surgery 24 hours			
Informed Consent/HIPAA	X							
Inclusion/Exclusion Criteria	X	X						
Medical & Surgical History	X	X						
Concomitant Medications	X	X	X	X	X	X	X	X
Ophthalmological Exam <sup>2</sup>	X <sup>2</sup>				X	X	X	X <sup>2</sup>
Slit Lamp Examination <sup>2</sup>	X <sup>2</sup>				X	X	X	X <sup>2</sup>
Visual Acuity Assessment	X <sup>2</sup>				X	X	X	X <sup>2</sup>
Intraocular Pressure (IOP)	X <sup>2</sup>				X	X	X	X <sup>2</sup>
Adverse Events		X	X		X	X	X	X
Randomization		X						
Treatment with Study Solution			X					
Cataract Extraction with or without lens replacement			X					
Vital Signs <sup>3</sup>			X					
Video Capture			X					
Ocular Pain (Alder Hey Triage Pain Score) <sup>4</sup>				X	X			
Removal of eye patch					X			
Collection and review of pain diary					X			

<sup>1</sup> Visit windows for subject contact are as follows: +/-30 minutes for subject diary entries at 3, 6, 9 and 24 hours for the postoperative Alder Hey Triage Pain Score, +/- 1 day for Day 8 postoperative visits, +/-2 days for Day 22-29 postoperative visits and +/- 7 days for the day 90 postoperative visits.

<sup>2</sup> (1) Examination of the lid, lashes and lacrimal apparatus, (2) Pupillary function, (3) Examination of the fundus (if possible), (4) Slit lamp examination (if possible – Appendix 19.3) of lids, lashes, conjunctiva, sclera, cornea, anterior chamber, iris, lens and anterior vitreous. Dilation with phenylephrine is allowed at all study-required time points for fundal examination.

<sup>3</sup> Vital Signs: Intra-operative (BP and HR after subject under anesthesia and every 10 minutes during procedure); Postoperative (BP and HR every 15 minutes in recovery room).

<sup>4</sup> Parent or legal guardian will complete pain diary at approximately 3, 6, 9 and 24 hours after surgery.

<sup>5</sup> Ophthalmic procedures required at Screening and Day 90 should be performed on both eyes. Ophthalmic procedures performed at other visits should be performed on the study eye only.

## 6 Review of Efficacy

### Efficacy Summary

#### 6.1 Indication

For the [REDACTED] (b) (4), prevention of intraoperative miosis, and reduction of [REDACTED] (u) (4) postoperative ocular pain

##### 6.1.1 Methods

Use of Omidria 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 12 Subject Demographics (Full Analysis Set)**

	PE (N = 39)	OMS302 (N = 33)	Total (N = 72)
Age (years)			
n	39	33	72
Mean (SD)	1.4 (1.2)	1.0 (1.1)	1.2 (1.2)
Median	0.9	0.5	0.7
Min, Max	0.1, 3.6	0.1, 3.9	0.1, 3.9
Gender, n (%)			
Male	20 (51%)	17 (52%)	37 (51%)
Female	19 (49%)	16 (48%)	35 (49%)
Ethnicity, n (%)			
Hispanic or Latino	10 (26%)	0	10 (14%)
Not Hispanic or Latino	29 (74%)	33 (100%)	62 (86%)
Race, n (%)			
American Indian or Alaska Native	0	0	0
Asian	0	1 (3%)	1 (1%)
Black or African American	3 (8%)	5 (15%)	8 (11%)
Native Hawaiian or Other Pacific Islander	0	0	0
White	30 (77%)	26 (79%)	56 (78%)
Other	6 (15%)	1 (3%)	7 (10%)

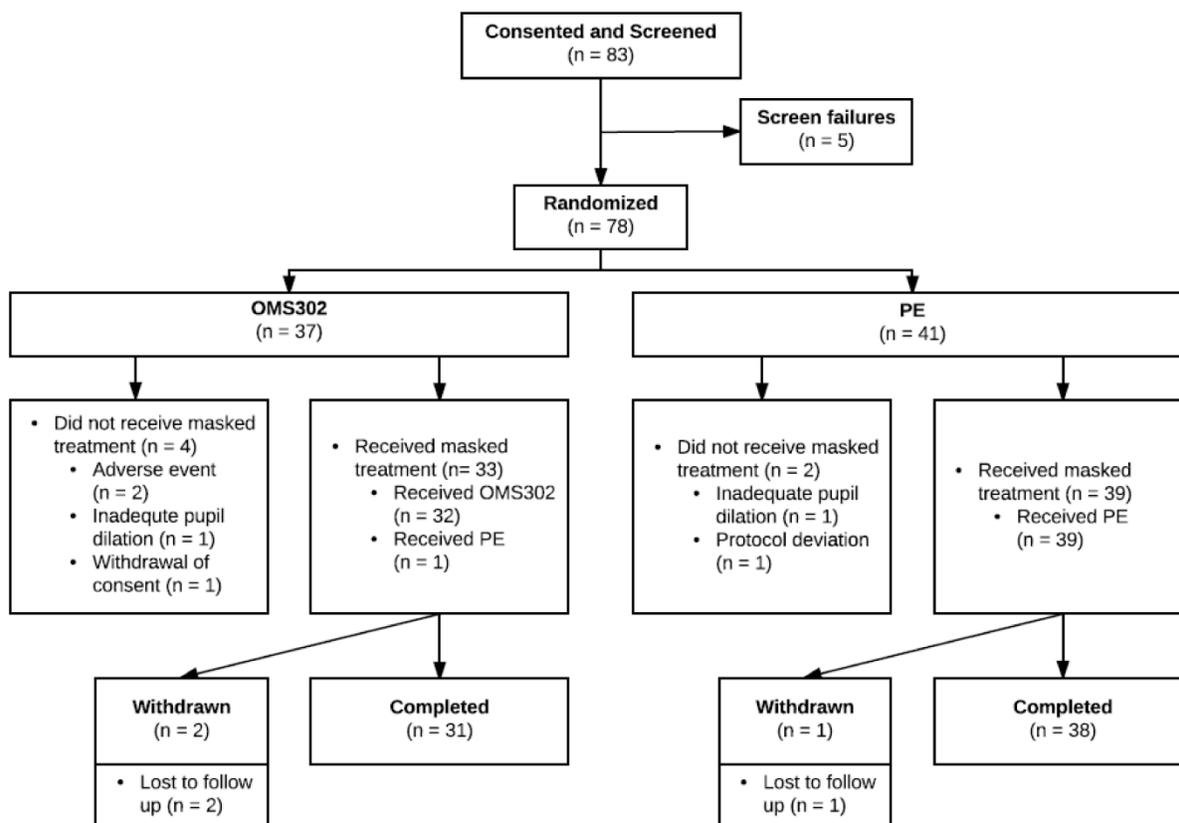
Source: [Section 14.1, Table 23](#)

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

**Figure 2 Disposition of Subjects**



Source: Section 14.1, Table 19, and Appendix 16.2.1.1 and Appendix 16.2.3.1

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: with drawn 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 9 Subject Disposition (Randomized Subjects)**

	<b>PE (N = 41) n (%)</b>	<b>OMS302 (N = 37) n (%)</b>	<b>Total (N = 78) n (%)</b>
Number of Subjects Randomized	41 (100%)	37 (100%)	78 (100%)
Number of Subjects That Received Study Treatment <sup>a</sup>	39 (95.1%)	33 (89.2%)	72 (92.3%)
Reason for Study Discontinuation			
Completed Study	38 (92.7%)	31 (83.8%)	69 (88.5%)
Lost to Follow-Up	1 (2.4%)	2 (5.4%)	3 (3.8%)
Other <sup>b</sup>	2 (4.9%)	4 (10.8%)	6 (7.7%)

<sup>a</sup> “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.

<sup>b</sup> “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 13 Mean Area-under-the-Curve (AUC) Analysis of Change from Baseline in Pupil Diameter (mm) during Surgery (Full Analysis Set)**

	PE (N = 39)	OMS302 (N = 33)
Mean AUC <sup>a</sup>		
n with video data	32	31
Mean (SD)	0.22 (0.601)	0.16 (0.480)
Median	0.15	0.18
Min, Max	-0.88, 2.36	-0.94, 1.40
Difference in Mean AUC		
CMH weighted mean difference (SE) <sup>b</sup>	-0.071 (0.131)	—
95% confidence interval	-0.327, 0.186	—
p-value <sup>c</sup>	0.5990	—

<sup>a</sup> AUC is calculated by the trapezoidal rule from the baseline to the last post-baseline value. Mean AUC is calculated by dividing the AUC by the duration from the baseline to the post-baseline value.

<sup>b</sup> CMH weighted mean difference (OMS302 – PE) is adjusted for the randomized IOL implant status.

<sup>c</sup> p-value is based on the generalized CMH test stratified by the randomized IOL implant status.

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.*

**Table 14 Mean Area-under-the-Curve (AUC) Analysis of Postoperative Alder Hey Triage Pain Score (Full Analysis Set)**

	<b>PE (N = 39)</b>	<b>OMS302 (N = 33)</b>
Mean AUC <sup>a</sup>		
n	38	33
Mean (SD)	0.65 (0.943)	0.44 (0.742)
Median	0.32	0.09
Min, Max	0.00, 4.16	0.00, 3.00
Difference in Mean AUC		
CMH weighted mean difference (SE) <sup>b</sup>	-0.214 (0.197)	—
95% confidence interval	-0.600, 0.172	—
p-value <sup>c</sup>	0.2874	—

<sup>a</sup> AUC is calculated by the trapezoidal rule from the first value to the last value. Mean AUC is calculated by dividing the AUC by the duration from the first value to the last value.

<sup>b</sup> CMH weighted mean difference (OMS302 – PE) is adjusted for the randomized IOL implant status.

<sup>c</sup> p-value is based on the generalized CMH test stratified by the randomized IOL implant status.

Source: [Section 14.2, Table 33](#)

## 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 18 Severe Adverse Events (Safety Population)**

<b>Preferred Term</b>	<b>PE (N = 40) n (%)</b>	<b>OMS302 (N = 32) n (%)</b>
Any Severe Adverse Event	0	3 (9.4%)
Bronchiolitis	0	1 (3.1%)
Respiratory Syncytial Virus Infection	0	1 (3.1%)
Vesicoureteric Reflux	0	1 (3.1%)

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)**

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

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Date: March 6, 2017 2:51 PM

**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

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: 17 sites		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
<p>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)): N/A</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study:</p> <p>Significant payments of other sorts:</p> <p>Proprietary interest in the product tested held by investigator:</p> <p>Significant equity interest held by investigator in sponsor of covered study:</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant) N/A
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)

Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: N/A	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

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*.<sup>1</sup> 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.

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<sup>1</sup> See [web address].

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Omidria® safely and effectively. See full prescribing information for Omidria.

**Omidria® (phenylephrine and ketorolac intraocular solution) 1% / 0.3%, for addition to ocular irrigating solution**  
Initial U.S. Approval: 2014

### 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)

### DOSAGE FORMS AND STRENGTHS

Intraocular solution containing phenylephrine 10.16 mg/mL (1%) and ketorolac 2.88 mg/mL (0.3%) for use in a single patient. (3)

### 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 ( $\geq 2\%$ ) 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](http://www.fda.gov/medwatch).

See 17 for PATIENT COUNSELING INFORMATION

Revised: XXXX/2017

## FULL PRESCRIBING INFORMATION: CONTENTS\*

<b>1</b>	<b>INDICATIONS AND USAGE</b>	<b>10</b>	<b>OVERDOSAGE</b>
<b>2</b>	<b>DOSAGE AND ADMINISTRATION</b>	<b>11</b>	<b>DESCRIPTION</b>
<b>3</b>	<b>DOSAGE FORMS AND STRENGTHS</b>	<b>12</b>	<b>CLINICAL PHARMACOLOGY</b>
<b>4</b>	<b>CONTRAINDICATIONS</b>	12.1	Mechanism of Action
<b>5</b>	<b>WARNINGS AND PRECAUTIONS</b>	12.3	Pharmacokinetics
5.1	Elevated Blood Pressure	<b>14</b>	<b>CLINICAL STUDIES</b>
5.2	Cross-Sensitivity or Hypersensitivity	<b>16</b>	<b>HOW SUPPLIED/STORAGE AND HANDLING</b>
<b>6</b>	<b>ADVERSE REACTIONS</b>	<b>17</b>	<b>PATIENT COUNSELING INFORMATION</b>
6.1	Clinical Studies Experience		
<b>8</b>	<b>USE IN SPECIFIC POPULATIONS</b>		
8.1	Pregnancy		
8.2	Lactation		
8.4	Pediatric Use		
8.5	Geriatric Use		

\*Sections or subsections omitted from the full prescribing information are not listed.

## **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**

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

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. Ketorolac 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  $C_{max}$ ) 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:

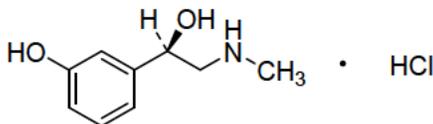
### **Phenylephrine Hydrochloride Drug Substance:**

**Common Name:** phenylephrine hydrochloride  
**Chemical Name:** (-)-*m*-Hydroxy- $\alpha$ -[(methylamino)methyl]benzyl alcohol hydrochloride

**Molecular Formula:** C<sub>9</sub>H<sub>13</sub>NO<sub>2</sub> · HCl

**Molecular Weight:** 203.67 g/mole

**Figure 1: Chemical Structure for Phenylephrine HCl**



**Ketorolac Tromethamine Drug Substance:**

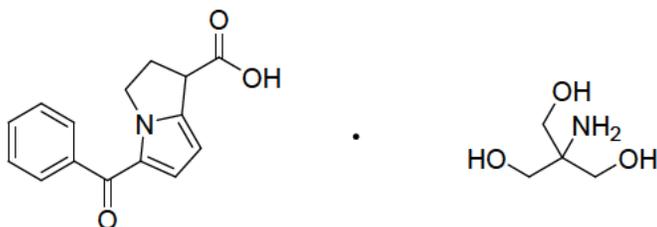
**Common Name:** ketorolac tromethamine

**Chemical Name:** (±)-5-Benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid : 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1)

**Molecular Formula:** C<sub>15</sub>H<sub>13</sub>NO<sub>3</sub> · C<sub>4</sub>H<sub>11</sub>NO<sub>3</sub>

**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  $\alpha_1$ -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

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**

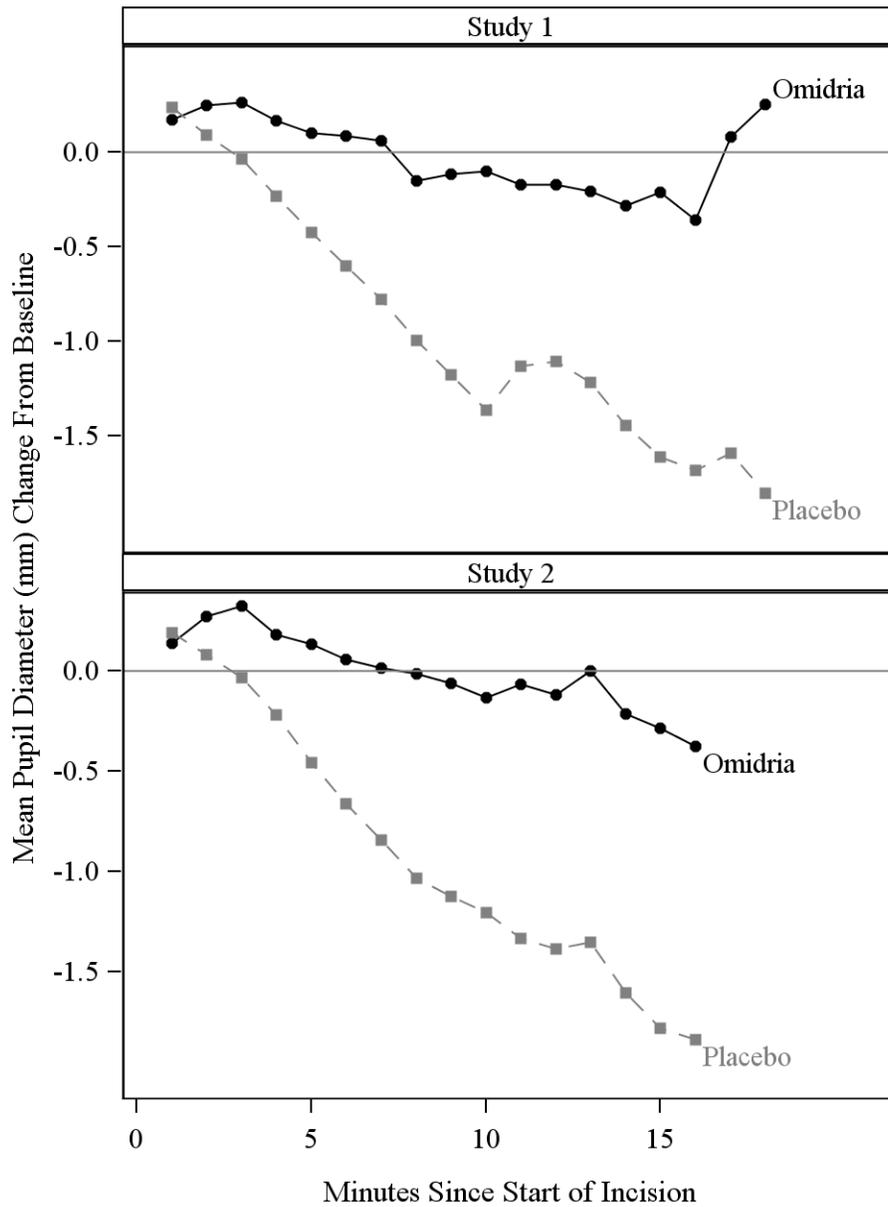
### **Studies in Adults**

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.

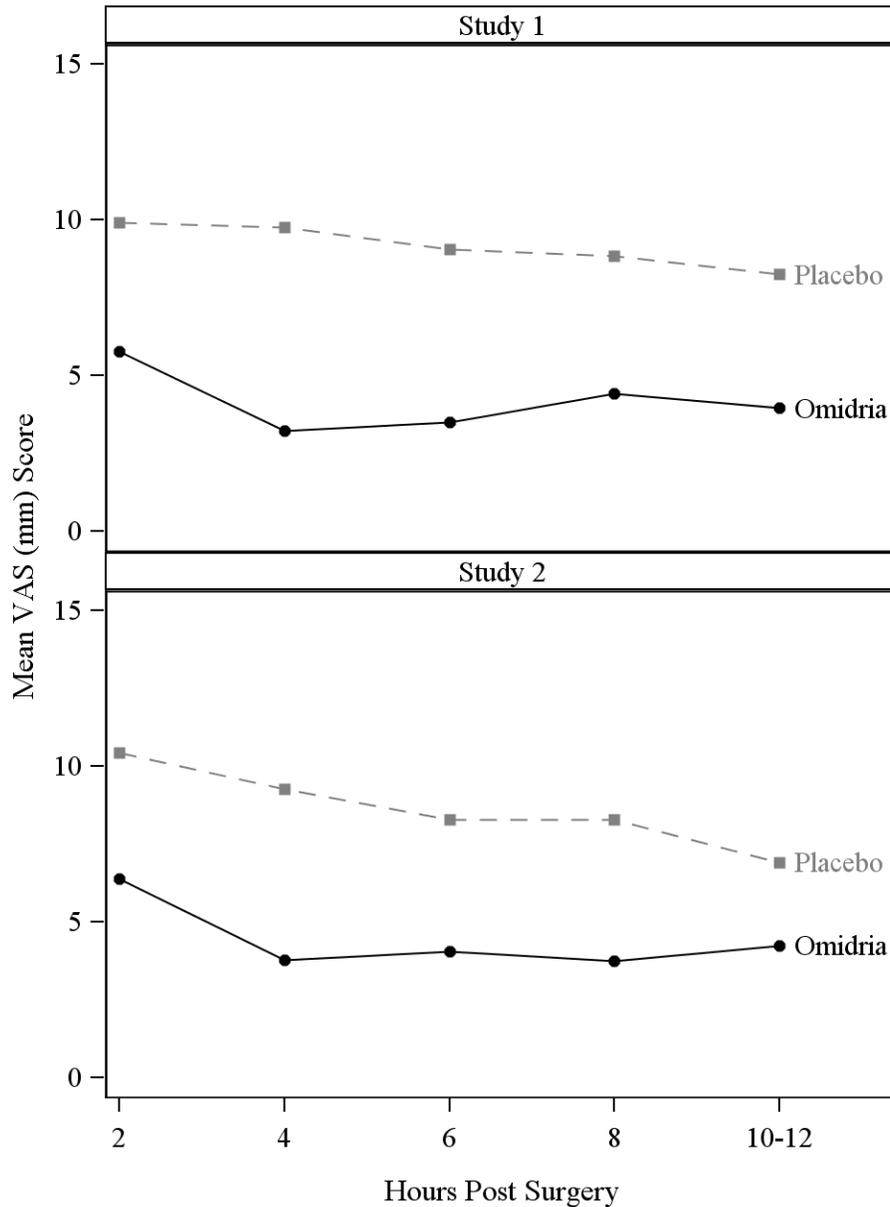
**Figure 3: Intraoperative Pupil Diameter (mm) Change-from-Baseline**



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.

Omeros Corporation  
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US Patents 8,173,707, 8,586,633, 9,066,856, 9,278,101, 9,399,040, and 9,486,406; additional patents pending.  
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Revised: XXXX/2017



Draft revised vial label is acceptable.



Draft revised carton label is acceptable.

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/s/  
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WILLIAM M BOYD  
12/05/2017

WILEY A CHAMBERS  
12/05/2017