Cross-Discipline Team Leader and Deputy Division Director (DTOP) Summary Review of NDA 205388/S-006

Date	December 4, 2017
From	William M. Boyd, M.D.; Wiley Chambers, M.D.
Subject	Cross-Discipline Team Leader and Deputy Division Director Summary Review
NDA/BLA # and Supplement#	NDA 205388/S-006
Applicant	Omeros
Date of Submission	June 9, 2017
PDUFA Goal Date	December 9, 2017
Proprietary Name	Omidria
Established or Proper Name	phenylephrine/ketorolac intraocular solution
Dosage Form(s)	Intraocular solution
Applicant Proposed Indication(s)/Population(s)	Indicated for maintaining pupil size by preventing intraoperative miosis and reducing postoperative ocular pain The safety and effectiveness of Omidria have been established in the pediatric population from neonates to adolescents (birth to younger than 17 years)
Applicant Proposed Dosing Regimen(s)	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
Recommendation on Regulatory Action	Approval

1. Benefit-Risk Assessment

Omidria (i.e., OMS302) is a fixed-dose combination product containing phenylephrine hydrochloride (PE), an α_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 2167-1and respond to the Written Request.

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Omidria (i.e., OMS302) is a fixed-dose combination product containing phenylephrine hydrochloride (PE), an α_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.

The clinical studies contained in this submission support the use of Omidria for the (b) (4) prevention of intraoperative miosis) and reduction of (b) (4) post-operative pain in the pediatric population from neonates to adolescents (birth to younger than 17 years).

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).

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

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Phenylephrine hydrochloride (PE) is an α1-adrenergic receptor agonist • Ketorolac tromethamine (KE), a non-selective cyclooxygenase (COX) COX-1/COX-2 inhibitor	α1-adrenergic receptor agonists are effective in th (b) (4) prevention of intraoperative miosis) Non-selective cyclooxygenase (COX) COX-1/COX-2 inhibitors are effective in the reduction of (b) (4) post-operative pain
Current Treatment Options	• Epinephrine can be added to ocular irrigating solution to assist in the (b) (4), but there are no other approved fixed-dose combination products that (b) (4) andreduce (b) (4) post-operative pain	There are no other approved fixed-dose combination products that (b) (4) andreduce (b) (4) post-operative pain
Benefit	• The clinical studies submitted at time of original product approval support the use of Omidria for the (b) (4) prevention of intraoperative miosis) and reduction of (b) (4) post-operative pain in adults.	This combination is safe and effective for use in standard irrigation solution used during cataract surgery.
Risk and Risk Management	• No risk management activities are recommended beyond the routine monitoring and reporting of all adverse events. There are no recommended Postmarketing Requirements or Phase 4 Commitments.	Routine monitoring and reporting of all adverse events are adequate.

2. Background

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.

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

3. Product Quality

See the original Product Quality review finalized 4/22/2014 and the review of this supplement, finalized 7/25/2017.

There is no new Chemistry Manufacturing and Controls information submitted in this supplemental application. The original application requested and justified a request for categorical exclusion, and the request was granted. Since this supplemental application does not differ from the original with respect to EA, this response is acceptable.

4. Nonclinical Pharmacology/Toxicology

See the original Pharmacology/Toxicology Review finalized 4/21/2014 and the review of this supplement, finalized 10/19/2017.

No new nonclinical studies were submitted with this supplement. As such, there are no new concerns from the nonclinical perspective.

In SD # 170, Omeros provided a revised label in PLR format. The Division sent an information request (dated 6-28-2017) to the applicant to submit the label in PLLR format. In SD # 174, Omeros resubmitted the label in PLLR format.

5. Clinical Pharmacology

See the original Clinical Pharmacology Review finalized 4/22/2014.

No new Clinical Pharmacoogy studies were submitted with this supplement.

6. Clinical Microbiology

Not applicable. This product is not an anti-infective.

7. Clinical/Statistical- Efficacy

Table 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 intracameral perfusion	78 (37 OMS302, 41 PE)	Pediatric subjects (0 to 3 years) undergoing cataract extraction with or without lens replacement	Single Dose

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.

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[a]		
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)[b]	-0.071 (0.131)	—
95% confidence interval	-0.327, 0.186	—
p-value[c]	0.5990	—

[a] 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.
[b] CMH weighted mean difference (OMS302 – PE) is adjusted for the randomized IOL implant status.
[c] p-value is based on the generalized CMH test stratified by the randomized IOL implant status.

Source: Section 14.2, Table 30

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

POSTOPERATIVE PAIN

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

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

	PE (N = 39)	OMS302 (N = 33)
Mean AUC[a]		
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)[b]	-0.214 (0.197)	—
95% confidence interval	-0.600, 0.172	—
p-value[c]	0.2874	—

[a] 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.
[b] CMH weighted mean difference (OMS302 – PE) is adjusted for the randomized IOL implant status.
[c] p-value is based on the generalized CMH test stratified by the randomized IOL implant status.

Source: Section 14.2, Table 33

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

Summary Efficacy Statement

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.

8. Safety

DEATHS

No subject deaths occurred during this study.

SIGNIFICANT ADVERSE EVENTS

Table 18 Severe Adverse Events (Safety Population)

Preferred Term	PE (N = 40) n (%)	OMS302 (N = 32) n (%)
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.

COMMON ADVERSE EVENTS

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

Preferred Term	PE (N=40) n(%)	OMS302 (N=32) n(%)
Any Event	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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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.

Safety Summary Statement

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).

9. Advisory Committee Meeting

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

10. Pediatrics

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**.**

11. Other Relevant Regulatory Issues

BIOSTATISTICS

See the Biostatistics review of this supplement dated 11/21/2017.

In the approval letter of 2014, the Agency required the applicant to submit a pediatric assessment study before September 30, 2017, under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c). The applicant conducted the required pediatric study (Study OMS302-ILR-007) and submitted the study report in this supplement. The supplement was also intended to

support a Pediatric Exclusivity requirement and the corresponding labeling change for Omidria.

The safety and efficacy of Omidria in pediatric patients was evaluated in one active-controlled clinical trial: OMS302-ILR-007 (referred to as Study 007 throughout this review). Study 007 was a randomized, parallel-group, double-masked, phenylephrine(PE)-controlled study of OMS302 in young children aged birth through 3 years undergoing unilateral cataract extraction with or without lens replacement. Prior to surgery, all subjects received standard of care to dilate their pupils. Study treatment was administered as irrigation solution to the anterior chamber of the eye during surgery to maintain mydriasis throughout the surgery. Postoperatively, all subjects received topical ophthalmic dexamethasone 0.1% and a topical ophthalmic antibiotic as prescribed by the subject's surgeon. The protocol-defined primary efficacy 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) determined by video capture during cataract surgery.
- Postoperative ocular pain as measured by the Alder Hey Triage Pain Score at 3, 6, 9, and 24 hours after surgery.

The mean duration of surgery was 35 minutes for OMS302 group and 40 minutes for PE group; the median duration of surgery was 37 minutes and 39 minutes for OMS302 and PE respectively. Approximately 80% subjects completed the surgical procedure by 40 minutes. Mydriasis was maintained throughout surgery in both treatment groups (Figure 1). At the baseline, the mean pupil diameter was about 7 mm in both OMS302 and PE groups. During the surgery, the mean change from baseline of pupil diameter ranged from -0.92 to 0.74 mm in the OMS302 group, and from -1.14 to 0.47 mm in the PE group. The mean area-under-the curve was 0.16 mm for the OMS302 group and 0.22 mm for the PE group (Table 1); the treatment difference was -0.07 mm with a 95% confidence interval (CI) of (-0.33, 0.19).

OFFICE OF PRESCRIPTION DRUG PROMOTION (OPDP)

The Office Of Prescription Drug Promotion (OPDP) completed a formal labeling review dated 11/20/2017. They also participated in the 11/17/2017, review team labeling meeting.

FINANCIAL DISCLOSURE

The applicant has adequately disclosed financial arrangements with clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical Investigators.*

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.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI)
Per the Office of Scientific Investigations review completed on 10/27/2017:

An inspection was requested for the following protocol in support of this application:

Protocol OMS302-ILR-007, "A Randomized, Double-Masked, Parallel-Group, Phenylephrine-Controlled Study of the Effect of OMS302 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."

This study involved 16 investigators at 14 domestic sites enrolling at least one subject for a total of 78 randomized subjects. Dr. Wilson's clinical site was chosen because of its relatively high enrollment and lack of recent inspection.

Site #/ Name of CI/ Address	**Protocol #/ # of Subjects (enrolled)**	**Inspection Dates**	**Classification**
Site #242 M. Edward Wilson, M.D. Medical University of South Carolina Storm Eye Institute 167 Ashley Avenue, Room 218 Charleston, SC 29425	OMS302-ILR-007 Subjects: 14	19-21 Sep 2017	NAI

Key to Compliance Classifications

NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.

This study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

12. Labeling

NDA 205388/S-006 is recommended for approval with the revised labeling identified in this review (submitted 12/4/2017). The clinical studies contained in this submission support the use of Omidria for the (b) (4) prevention of intraoperative miosis) and reduction of (b) (4) post-operative pain in the pediatric population from neonates to adolescents (birth to younger than 17 years).

13. Postmarketing Recommendations

There are no risk management activities recommended beyond the routine monitoring and reporting of all adverse events. There are no recommended Postmarketing Requirements or Phase 4 Commitments.

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 (≥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: CONTENTS*

*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 ≥ 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 ≥ 2% of Adult Patients

MedDRA Preferred Term	Placebo (N=462)	Omidria (N=459)
	n (%)	n (%)
Ocular Events		
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. Howerver, 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

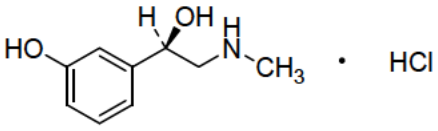
Omidria is a sterile aqueous solution, containing the α_1-adrenergic receptor agonist phenylephrine HCl and the nonsteroidal anti-inflammatory ketorolac tromethamine, for addition to ocular irrigating solution.

The descriptions and structural formulae are:

Phenylephrine Hydrochloride Drug Substance:

Common Name:	phenylephrine hydrochloride
Chemical Name:	(-)-*m*-Hydroxy-α-[(methylamino)methyl]benzyl alcohol hydrochloride
Molecular Formula:	$C_9H_{13}NO_2 \cdot HCl$
Molecular Weight:	203.67 g/mole

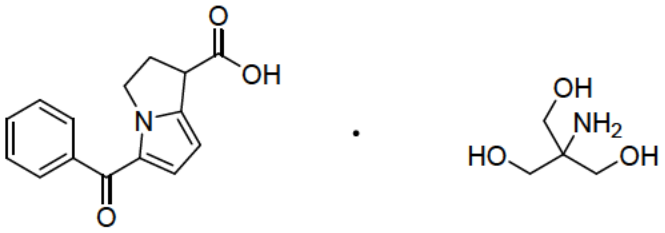
Figure 1: Chemical Structure for Phenylephrine HCl



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:	$C_{15}H_{13}NO_3 \cdot C_4H_{11}NO_3$
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 α_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

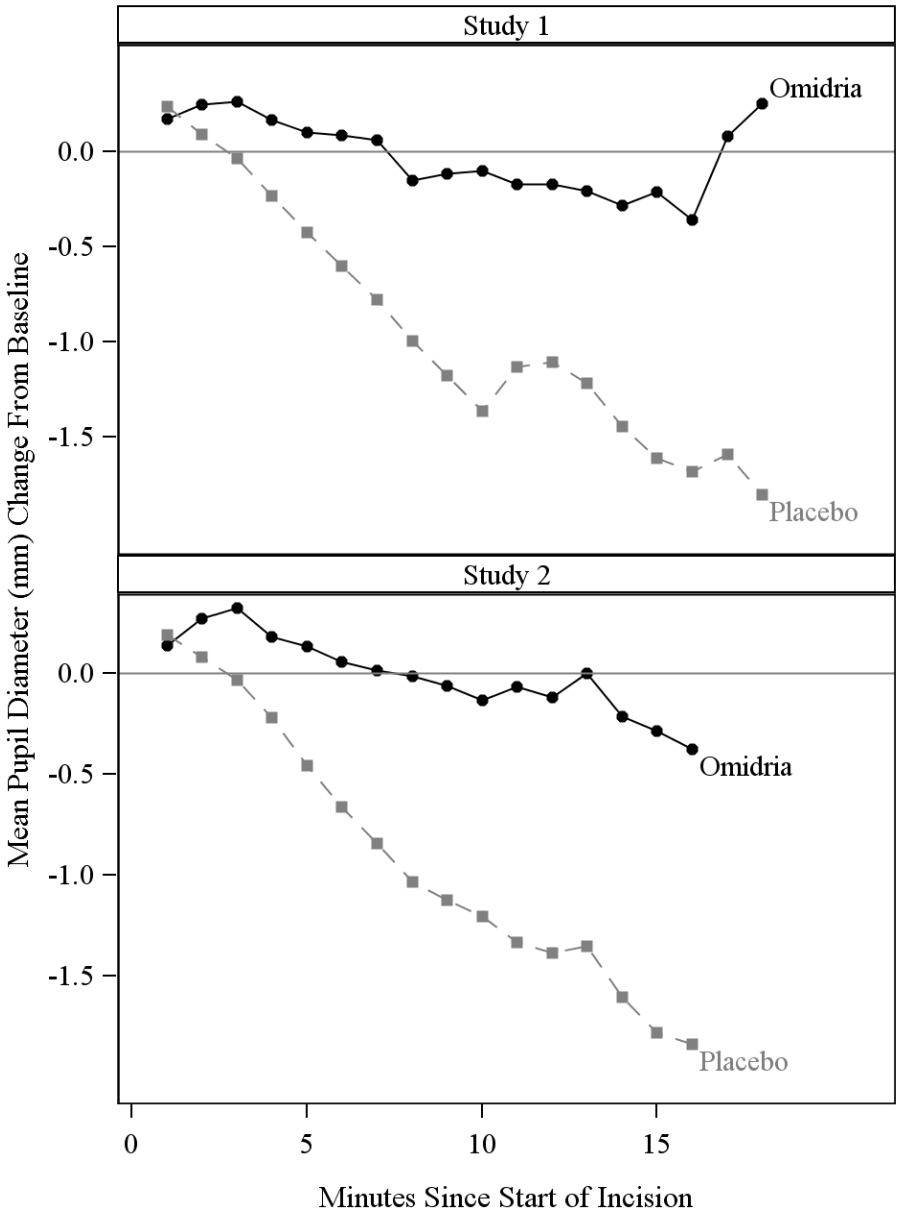
Studies in Adults

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.

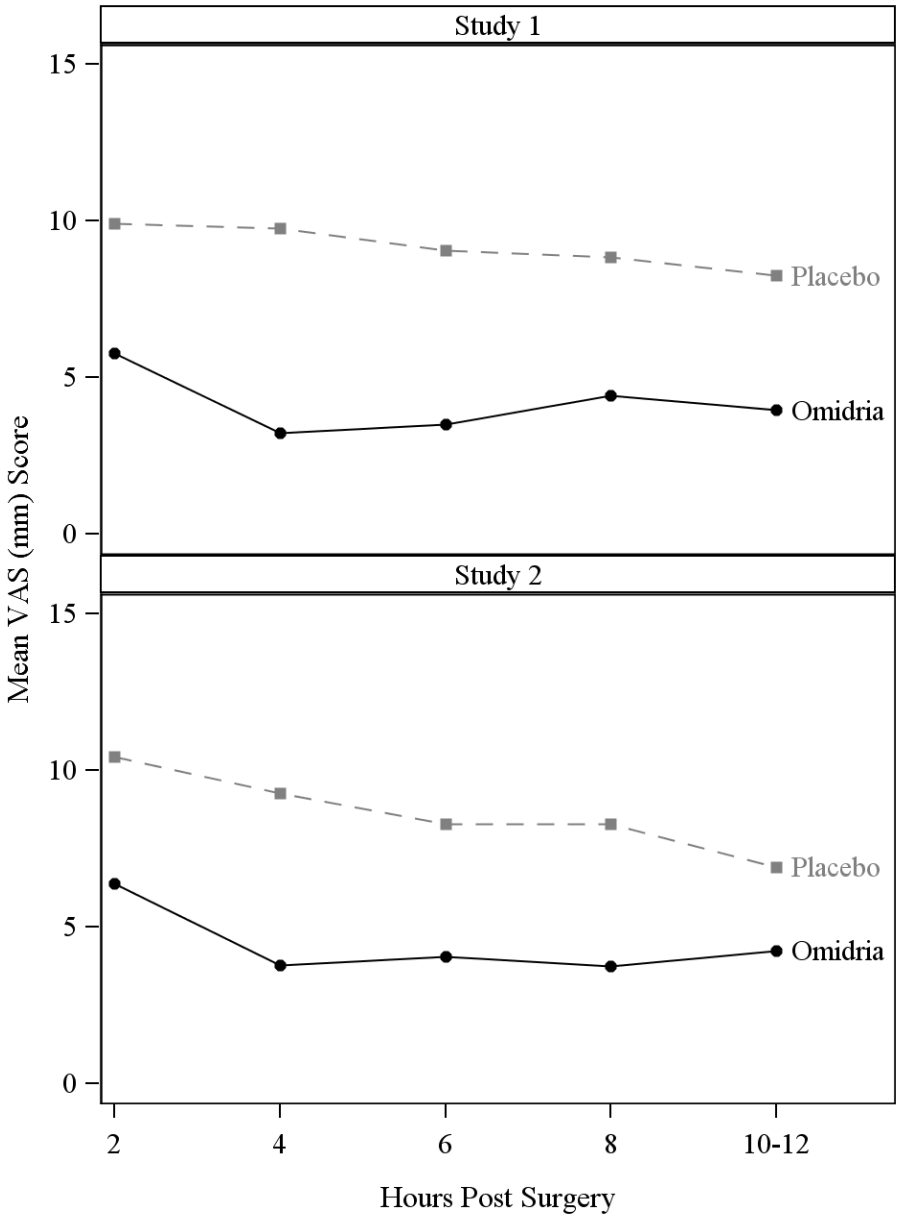
Figure 3: Intraoperative Pupil Diameter (mm) Change-from-Baseline



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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Seattle, WA 98119

PI100016

Revised: XXXX/2017

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