CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205388Orig1s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Renata Albrecht, MD
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	NDA 205388 N/A
Related IND	IND 78227
Applicant Name	Omeros Corporation
Application Type	505(b)(2)
Date of Submission	7/30/2013 (standard review)
PDUFA Goal Date	5/30/2014
Proprietary Name / **Established (USAN) Name**	Omidria phenylephrine and ketoroloc injection
Dosage Forms / Strength	solution 1%/0.3%
Preservative	None
Route of Administration	Intraocular/intracameral
Therapeutic Class	alpha 1-adrenergic receptor agonist (sympathomimetic) and nonselective cyclooxygenase inhibitor (NSAID)
Proposed Indication(s)	for maintaining pupil size by preventing intraoperative miosis and reducing postoperative ocular pain.
Dosage Regimen	4 mL of Omidria is diluted in 500 mL of ophthalmic irrigation solution to be used as needed for the surgical procedure
How Supplied	sterile solution concentrate (4 mL) containing 10.16 mg/mL (1% w/v) of phenylephrine and 2.88 mg/mL (0.3% w/v) of ketorolac in a clear, 5-mL glass, single-patient use vial
Action	*Approval*

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Sonal Wadhwa, William Boyd 5/9/2014
CDTL Review	William Boyd 5/27/2014
Deputy Director's Review	Wiley Chambers 5/27/2014
Statistical Review	Yunfan Deng, Yan Wang 4/25/2014
Pharmacology Toxicology Review	Maria Rivera, Lori Kotch 4/21/2014
CMC Review	Mark Seggel, Rapti Madurawe 4/22/2014, 5/30/14
Quality Microbiology Review	Steven Donald, Stephen Langille 12/16/2013
Biopharmaceutics Review	Houda Mahayni, Angelica Dorantes 12/8/2013
Office of Compliance	Acceptable 5/30/2014 EES
Clinical Pharmacology Review	Yoriko Harigaya, Philip Colangelo 4/22/2014
OPDP/DPDP	Christine Corser 4/14/2014
OSI/DGCPC	Roy Blay, Janice Pohlman, Kassa Ayalew 4/14/2014
OSE/DMEPA Proprietary Name Letter	Aleksander Winiarski, Morgan Walker, Carol Holquist 11/8/2013 Kellie Taylor 11/15/2013
OSE/DMEPA	Rachna Kapoor, Yelena Maslov 4/7/2014
OSE/DDRE	N/A
OSE/DRISK	N/A
Project Manager	Jacquelyn Smith

OND=Office of New Drugs
CDTL=Cross-Discipline Team Leader
OSI/DGCPC=Office of Scientific Investigations/Division of Good Clinical Practice Compliance
OPDP/DPDP=Office of Prescription Drug Promotion/Division of Prescription Drug Promotion
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management

Signatory Authority Review Template

1. Introduction

Omidria is a combination product containing 10.16 mg/mL (1% w/v) of phenylephrine and 2.88 mg/mL (0.3% w/v) of ketorolac in a single-patient-use vial.[1] Once the 4mL of Omidria is diluted in 500 mL of ophthalmic irrigation solution, the resulting solution is intended to be used as needed during cataract surgery or intraocular lens replacement. The combination product is indicated for maintaining pupil size by preventing intraoperative miosis and reducing postoperative ocular pain. There are currently no approved combination products for these two indications, and the individual products are not approved intracameral use for the individual indications. Topical phenylephrine (NDA 203510) is approved for pupil dilation, and topical ketorolac (NDA 19700) is approved for treatment of inflammation following cataract surgery and relief of ocular itching due to seasonal allergic conjunctivitis. Other formulations of ketorolac are also available: ACULAR LS (NDA 21528), is indicated for the reduction of ocular pain and burning/stinging following corneal refractive surgery. ACULAR (NDA 20811) is indicated for the treatment of postoperative inflammation in patients who have undergone cataract extraction. ACUVAIL (NDA 22427) is indicated for the treatment of pain and inflammation following cataract surgery. Systemic formulations of these products are also approved.

Approval of the current application NDA 205388 is supported by three controlled clinical trials:

- Protocol C09-001 evaluated the efficacy and safety of the combination product to each of the two components, phenylephrine HCl and ketorolac tromethamine to maintain mydriasis and relieve pain in patients with unilateral cataract extraction with lens replacement (CELR).
- Protocol OMS302-ILR-003 evaluated the efficacy and safety of the combination (Omidria) to placebo on pupil diameter and postoperative pain in patients with intraocular lens replacement with phacoemulsification.
- Protocol OMS302-ILR-004 was a second study, very similar in design to study -003.

The application is a 505(b)(2) application that relies on the agency's findings of safety and effectiveness from the topical NDA labeling, and on nonclinical studies bridging to the published literature.

2. Background

The product was developed under IND 78227. An end-of-phase 2 meeting was held July 15, 2011, the pre-NDA CMC meeting was on January 16, 2012, and the pre-NDA clinical meeting was on February 11, 2013.

[1] Omidria has been referred to as OMS302 during its development, and this name is also used in this review.

The product is submitted as a 505(b)(2) application, and the 505(b)(2) Assessment Form discusses the bridging from other information and NDAs to the current product:

> The listed drug products are both approved for topical ophthalmic use and there is extensive experience with the use of both phenylephrine and ketorolac as topical products in ophthalmology. To bridge the difference in dosage forms to be able to rely on the listed products and the literature, Omeros conducted three nonclinical pharmacology studies and one GLP safety and toxicology study. The nonclinical studies conducted by Omeros confirmed the pharmacology of the components of Omidria and assessed the potential toxicity of phenylephrine and ketorolac when administered intracamerally both separately and together as they are in Omidria.
>
> The applicant is also relying on the agency's general findings of safety and effectiveness for phenylephrine hydrochloride ophthalmic solution (NDA 203510) and Acular (ketorolac tromethamine ophthalmic solution) 0.5% (NDA 019700), but is not relying on NDA 19645.

3. CMC

For details, see the CMC, Quality Microbiology and Biopharmaceutic reviews. The following summary is based on these reviews.

Omidria is a sterile solution of phenylephrine HCl, a mydriatic agent, and ketorolac tromethamine, a nonsteroidal anti-inflammatory agent. Each vial contains the equivalent of 40.64 mg phenylephrine (1% w/v) and 11.51 mg ketorolac (0.3% w/v) in 4.0 mL of (b) (4), pH 6.3 sodium citrate (b) (4) The product is for single use and does not contain a preservative. Each vial is filled to allow withdrawal of 4.0 mL of formulation concentrate for admixture with 500 mL of ophthalmic irrigation solution.

The drug product is (b) (4) (b) (4) validation studies are considered adequate.

The drug product specifications provide additional assurance that Omidria has the purported identity, strength, quality, purity and potency. The specification includes tests for identity, pH, osmolality, assay, degradation products, sterility, endotoxins and particulate matter. CMC recommended tighter acceptance criteria for individual specified and unspecified degradants, and total degradants, and the acceptance criteria were tightened.

Available stability data support an 18-month expiration dating period for the drug product stored at 20°-25°C (68°-77°F) and protected from light. The diluted product can be stored for no more than 4 hours at room temperature or 24 hours under refrigerated conditions. Potential degradation of the actives in the drug product by, for example, oxidation and photodegradation, is mitigated by product manufacturing process controls and storage conditions.

The proposed commercial container closure system consists of a 5-mL Type 1 clear (b) (4) glass tubing vial and an elastomeric closure. Several extractables and leachables from the glass vials and elastomeric stoppers were identified but the levels observed are not expected to be of main toxicological concern for the proposed dose regimen, based on the P/T review. The applicant will continue leachables testing on product throughout its shelf life. The container closure integrity studies demonstrate the adequacy of the proposed container and closure to maintain the sterility of the drug product. The suitability of the sterility and endotoxin test methods has been adequately demonstrated.

The applicant performed a PK substudy in the Phase 3 Study OMS302- ILR-004 and the systemic exposure to phenylephrine and ketorolac was low or undetectable at all timepoints. The biowaiver request was granted.

The physical and chemical compatibility of Omidria with balanced salt solutions has been demonstrated (no loss of potency, increase in impurities, or formation of subvisible particulate matter contamination). This testing was considered sufficient.

The Office of Compliance has issued a recommendation of Acceptable for manufacturing facilities.

(b) (4)

Comment:
I concur with the conclusions reached by the chemistry reviewers regarding the acceptability of the manufacturing of the drug product. Manufacturing site inspections were acceptable. There are no outstanding CMC issues to preclude approval.

4. Nonclinical Pharmacology/Toxicology

For details, see the Pharmacology/Toxicology Review. A brief summary it provided below.

Phenylephrine and ketorolac both have a long history of use as topical agents in ophthalmology and there is a significant body of literature on their individual clinical pharmacology. The safety and efficacy data in support the use of OMS302 for the intended indication relies on historical data as well as nonclinical and clinical studies conducted with OMS302.

A single-dose toxicology study was conducted in African green monkeys exposed during lens replacement surgery to ocular irrigation solutions containing OMS302. No drug related ocular or systemic adverse findings were observed, with combinations of phenylephrine hydrochloride and ketorolac tromethamine in irrigation solution administered at concentrations up to 7200 μM and 900 μM, respectively. These concentrations are over 10-fold higher than the concentrations intended to be administered clinically (480 μM phenylephrine hydrochloride and 89 μM ketorolac tromethamine).

At the NOAEL dose in the ocular toxicology study, the maximal levels of phenylephrine and ketorolac were 7-fold and 4-fold higher in the anterior chamber, and 27-fold and 47-fold higher in the plasma, respectively, than the levels observed after administration of OMS302 in the clinic. The absence of any test article-related findings in assessment of ocular physiology and histopathology and systemic toxicity endpoints supports the safety of the product.

The application contains sufficient information and the labeling for Sections 8 and 13 has been revised

Comment:
I concur with the conclusions reached by the pharmacology/toxicology reviewers to recommend approval and the proposed labeling revisions which have been incorporated in labeling. There are no outstanding pharm/tox issues that preclude approval.

5. Clinical Pharmacology/Biopharmaceutics

For details, see the Clinical Pharmacology review. A brief summary is provided below.

The two active pharmaceutical ingredients (API) in Omidria, phenylephrine (PE) and ketorolac (KE), act to maintain pupil size by preventing intraoperative miosis, and reducing postoperative pain.
Phenylephrine is an αlpha1-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.[2]

[2] Of historical note, two ophthalmic NSAIDs were approved for the inhibition of intraoperative myosis: NDA 19404, and Ocufen (flurbiprofen) was approved 12/31/1986 and NDA 19-387, Profenal (suprofen) was approved 12/23/1988 .

OMS302 is a sterile solution concentrate containing 12.37 mg/mL (61 mM) of PE and 4.24 mg/mL (11 mM) of KE in a single-use vial. For administration, OMS302 must be diluted prior to use as follows: 4.0 mL of OMS302 drug product is diluted in 500 mL of an ophthalmic irrigation solution resulting in a solution with PE at a final concentration of approximately 480 μM (0.0098% w/v) and KE at a final concentration of approximately 89 μM (0.0034% w/v).

One clinical PK substudy was conducted to evaluate the systemic exposure to PE and KE following administration of Omidria during intraocular lens replacement surgery in 26 subjects (14 OMS302 vs. 12 placebo) in Study OMS302-ILR-004.

- PE plasma concentrations were detectable (range 1.2 to1.4 ng/mL) in one of 14 subjects [Lower Limit of Quantification (LLOQ) =1 ng/mL]. The systemic absorption of PE may have been due to application of preoperative PE ophthalmic solution, since the highest PE concentration observed (i.e., 1.7 ng/mL) was immediately following administration of pre-operative topical drops of PE 2.5% ophthalmic solution (i.e., at approximately 30 minutes, 15 minutes, and 5 minutes before surgery) and before OMS302 was administered.
- KE plasma concentrations were detected in 10 of 14 subjects (range 1.0 to 4.2 ng/mL), which were insufficient for PK analysis. The maximum KE concentration (i.e., 15.2 ng/mL) was observed at 24 hours after the initiation of Omidria administration, which may have been due to application of post-operative KE ophthalmic solution.

One Phase 1/2 exploratory Study C07-005 was conducted to evaluate safety and potential efficacy endpoints of PE alone vs. OMS302 vs. Vehicle. One Phase 2 Study C09-001was conducted to evaluate the separate contributions of PE and KE to the proposed indication.

Comment:
I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewers to recommend approval. There are no outstanding clinical pharmacology issues that preclude approval.

6. Clinical Microbiology

Not applicable

7. Clinical/Statistical-Efficacy

For details, see the Clinical and Statistical reviews. A brief summary is provided below.

Three controlled clinical trials support the approval of this application, and showed that Omidria is effective in maintaining pupil dilution during the intraocular lens replacement surgery compared to ketorolac (KE) and placebo and in reducing ocular pain during the first 12 hours postoperatively compared to phenylephrine (PE) and placebo.

Study C09-001 is a full-factorial safety and efficacy study that evaluated the contributions of phenylephrine and ketorolac to maintenance of mydriasis and relief of pain in patients

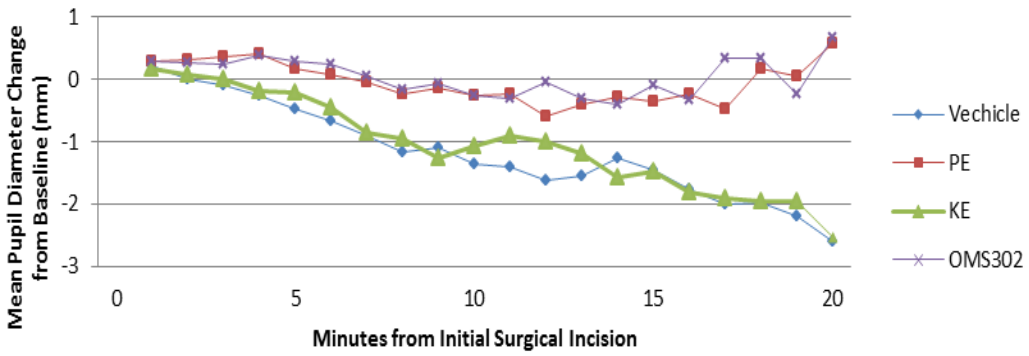
undergoing cataract surgery. A total of 222 subjects (56 in vehicle, 53 in PE, 56 in KE, and 56 in OMS302) were enrolled and treated at 23 centers across U.S. The co-primary efficacy endpoints were:

- The change in pupil diameter over time from surgical baseline (immediately prior to surgical incision) to the end of the surgical procedure (wound closure). Pupil diameters were captured from snapshots of video at intervals of one minute and were later measured by a masked central reader at each minute throughout the surgery.[3]

- Postoperative pain as measured by the Visual Analog Scale (VAS, ranging from 0 – 100) at 2, 4, 6, 8 and 10-12 hours of the end of surgery.

The study needed to demonstrate superiority of OMS302 versus KE and vehicle for mydriasis and superiority of OMS302 versus PE and vehicle for postoperative ocular pain. This study demonstrated the contribution of each component to the treatment effect.

Figure 1: Study C09-001 Intraoperative Pupil Diameter (mm) Mean Change-from-Baseline



Source: Statistical Review

Summary of Proportion of Patients with Zero Visual Analog Scale for Pain Scores Post-Surgery at Each Time Point for Study C09-001 (All Treated Subjects)

	Study C09-001		
	OMS302	**PE**	**Diff (95% CI)**
2 Hours	31/55 (56.4%)	28/56 (50.0%)	6.4% (-12.2%, 24.9%)
4 hours	26/49 (53.1%)	20/52 (38.5%)	14.6% (-4.6%, 33.8%)
6 Hours	29/55 (52.7%)	22/55 (40.0%)	12.7% (-5.8%, 31.2%)
8 Hours	27/51 (52.9%)	18/54 (33.3%)	19.6% (1.0%, 38.2%)
10 to 12 Hours	30/54 (55.6%)	18/55 (32.7%)	22.8% (4.7%, 41.0%)

* 95% CI based on chi-square test
Source: statistical reviewer's analysis and review

[3] See Clinical Reviews about exclusion from patients where technical difficulties prevented correct interpretation of pupil diameter.

Study OMS302-ILR-003 and Study OMS302-ILR-004 (referred to as Study 1 and Study 2 in labeling) both compared the effect of Omidria vs. placebo on intraoperative pupil diameter and post-operative pain in cataract surgery. The primary endpoint was pupil diameter; postoperative pain was a co-primary endpoint in Study OMS302-ILR-004; and the first secondary endpoint in Study OMS302-ILR-003. Both endpoints were analyzed based on mean area-under-curve (AUC) using a generalized Cochran-Mantel-Haenszel (CMH) test stratified by the randomization strata. The mean AUC was calculated by dividing the AUC (calculated by the trapezoidal rule over the time period) by the total time.

A total of 402 subjects were randomized and treated at 17 centers across U.S. in Study OMS302-ILR-003, 38 (9.5%) were excluded due to technical issues related to video recording (described in clinical review). In Study OMS302-ILR-004, 406 subjects were randomized and treated at 15 centers across U.S. and 11 (2.7%) were excluded from the pupil diameter analyses. All but two subjects were included in the analysis of pain.

In Study OMS302-ILR-003, the mean AUC estimate of change from baseline in pupil diameter was 0.1mm for OMS302 and -0.5mm for placebo; with treatment difference of 0.6 mm (95% CI: 0.5, 0.7). The mean AUC estimate of ocular pain VAS score was 4.1 for OMS302 and 9.2 for placebo; the treatment difference was -5.2 (95% CI: -7.3, -3.1).

In Study OMS302-ILR-004, the mean AUC estimate of change from baseline in pupil diameter was 0.1mm for OMS302 and - 0.5mm for placebo; with treatment difference of 0.6mm (95% CI: 0.5, 0.7). The mean AUC estimate of ocular pain VAS score was 4.3 for OMS302 and 8.9 for placebo; the treatment difference was -4.6 (95% CI: -6.9, -2.2).

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

The figures and table below are from the Statistical Review:

Studies OMS302-ILR-003 and OMS302-ILR-004 Treatment Difference in Change from Baseline of Mean Pupil Diameter (mm) at Each Time Point during CELR Surgery (Subjects with Readable Video Recordings)

	Study 003					Study 004				
	Placebo		OMS302		OMS302 vs. Placebo	Placebo		OMS302		OMS302 vs. Placebo
Time	n	Mean	n	Mean	Difference (95% CI)*	n	Mean	n	Mean	Difference (95% CI)*
1 minute	180	0.24	183	0.17	-0.07 (-0.17, 0.04)	200	0.19	194	0.13	-0.06 (-0.17, 0.05)
2 minute	179	0.09	184	0.25	0.16 (0.03, 0.28)	200	0.08	195	0.26	0.18 (0.06, 0.30)
3 minute	180	-0.04	184	0.26	0.30 (0.16, 0.44)	200	-0.03	195	0.32	0.35 (0.22, 0.48)
4 minute	180	-0.23	183	0.16	0.40 (0.25, 0.55)	200	-0.21	195	0.17	0.39 (0.26, 0.52)
5 minute	178	-0.42	184	0.10	0.52 (0.36, 0.68)	199	-0.46	190	0.13	0.59 (0.46, 0.73)
6 minute	169	-0.60	159	0.09	0.69 (0.52, 0.86)	182	-0.66	170	0.05	0.72 (0.56, 0.88)
7 minute	149	-0.78	130	0.06	0.84 (0.62, 1.06)	161	-0.84	140	0.00	0.84 (0.64, 1.05)
8 minute	123	-1.00	111	-0.15	0.85 (0.61, 1.08)	136	-1.03	114	-0.02	1.01 (0.80, 1.23)

9 minute	104	-1.18	94	-0.11	1.06 (0.75, 1.37)	101	-1.12	90	-0.07	1.05 (0.78, 1.33)
10 minute	87	-1.37	81	-0.10	1.27 (0.91, 1.62)	85	-1.21	75	-0.16	1.05 (0.73, 1.37)
11 minute	67	-1.13	66	-0.17	0.96 (0.59, 1.34)	67	-1.34	62	-0.09	1.24 (0.92, 1.57)
12 minute	55	-1.11	57	-0.17	0.94 (0.59, 1.28)	53	-1.39	53	-0.15	1.24 (0.82, 1.65)
13 minute	53	-1.22	50	-0.21	1.01 (0.63, 1.38)	47	-1.35	42	0.00	1.35 (0.90, 1.81)
14 minute	47	-1.45	43	-0.28	1.16 (0.74, 1.58)	39	-1.61	35	-0.22	1.39 (0.87, 1.92)
15 minute	36	-1.61	37	-0.21	1.40 (0.91, 1.89)	31	-1.79	27	-0.28	1.50 (0.88, 2.13)
16 minute	28	-1.68	27	-0.36	1.33 (0.68, 1.98)	23	-1.84	23	-0.38	1.46 (0.68, 2.24)
17 minute	23	-1.59	17	0.08	1.67 (1.03, 2.32)	19	-2.00	16	-0.40	1.59 (0.68, 2.51)
18 minute	21	-1.81	12	0.25	2.06 (1.27, 2.84)	15	-2.12	12	-0.45	1.67 (0.57, 2.76)
19 minute	16	-2.06	9	0.21	2.28 (1.39, 3.16)	12	-2.00	9	-0.43	1.58 (0.19, 2.97)
20 minute	15	-2.14	7	0.29	2.43 (1.42, 3.44)	9	-1.80	6	-0.85	0.96 (-0.98, 2.89)

* 95% CI based on two-sample t-test
Source: statistical reviewer's analysis and review.

Figure 2: Study OMS302-ILR-003 Intraoperative Pupil Diameter (mm) Mean Change-from-Baseline

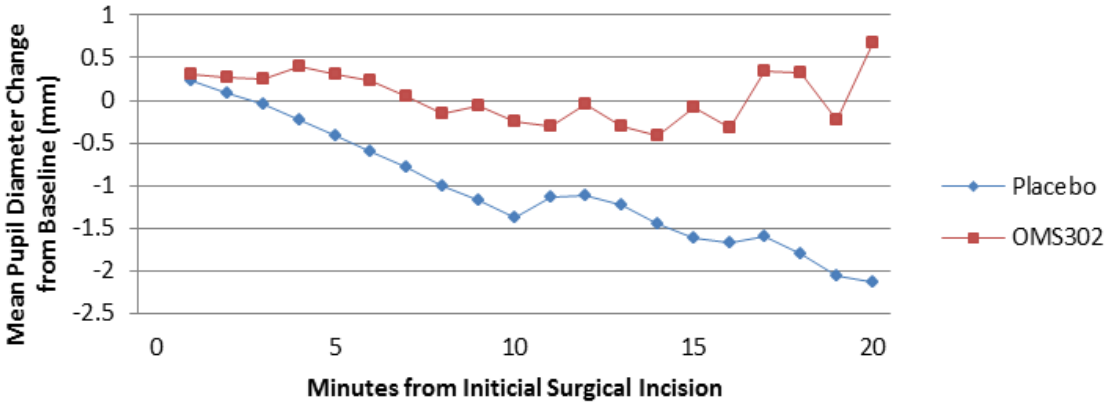
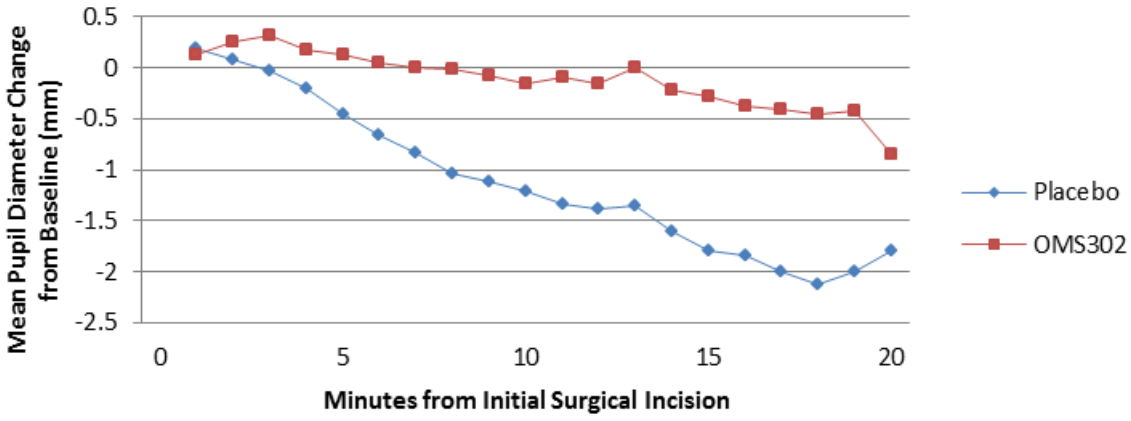


Figure 3: Study OMS302-ILR-004 Intraoperative Pupil Diameter (mm) Mean Change-from-Baseline



Proportion of Patients with Zero Visual Acuity Score for Pain Post-Surgery over Time for Studies OMS302-ILR-003 and OMS302-ILR-004 (All Treated Subjects)

	Study OMS302-ILR-003			Study OMS302-ILR-004		
	OMS302	Placebo	Difference (95% CI)*	OMS302	Placebo	Difference (95% CI)*
2 Hours	81/201 (40.3%)	61/201 (30.4%)	9.95% (0.7%, 19.2%)	101/202 (50.0%)	75/203 (37.0%)	13.1% (3.5%, 22.6%)
4 hours	94/201 (46.8%)	62/200 (31.0%)	15.8% (6.4%, 25.2%)	111/202 (55.0%)	80/203 (39.4%)	15.5% (5.9%, 25.2%)
6 Hours	91/201 (45.3%)	59/201 (29.4%)	15.9% (6.6%, 25.3%)	107/202 (53.0%)	80/203 (39.4%)	13.6% (3.9%, 23.2%)
8 Hours	94/201 (46.8%)	58/200 (29.0%)	17.8% (8.4%, 27.1%)	115/202 (56.9%)	84/201 (41.8%)	15.1% (5.5%, 24.8%)
10 to 12 Hours	92/201 (45.8%)	64/199 (32.2%)	13.6% (4.2%, 23.1%)	123/199 (63.3%)	89/202 (44.1%)	19.3% (9.7%, 28.8%)

* 95% CI calculated using chi-square test
Source: Statistical reviewer's analysis and review

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

Postoperative Mean Visual Analog Scale (VAS) Scores for Pain

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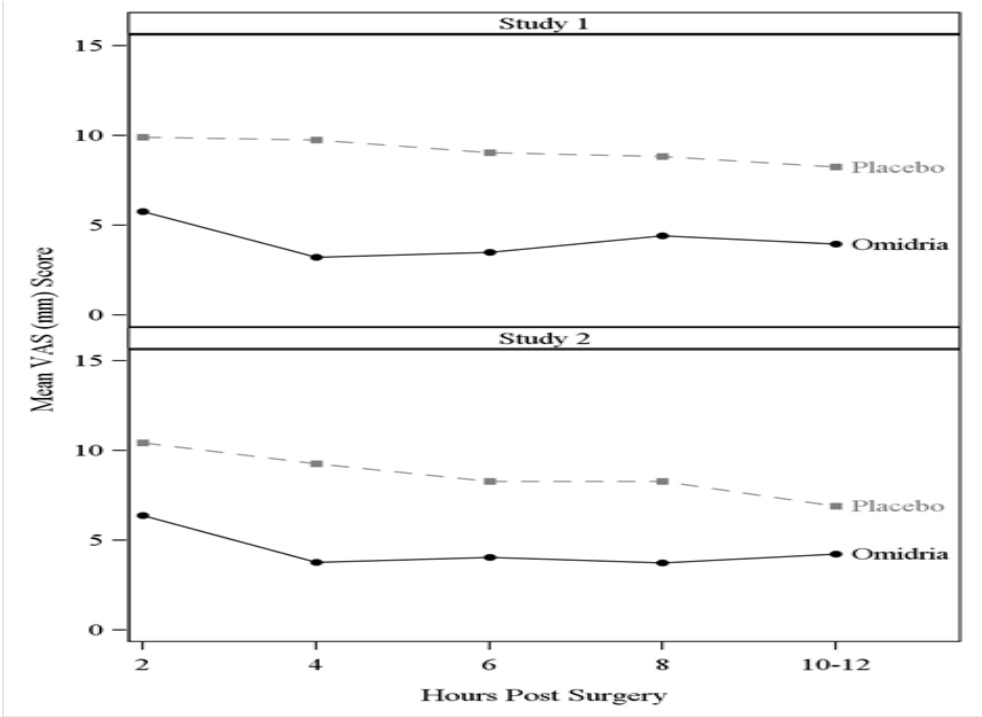

Comment:
I concur with the conclusions reached by the clinical and statistical reviewers that Omidria is effective in maintaining pupil size by preventing intraoperative miosis and reducing postoperative ocular pain during cataract surgery and intraocular lens replacement. There are no outstanding efficacy issues that preclude approval. The Clinical Studies section adequately summarizes the study design and efficacy outcomes.

8. Safety

For further details, see the Clinical and Statistical Reviews. A brief summary is provided below.

A total of 403 Omidria patients and 405 placebo patients participated in the two Phase 3 studies, and received on average around 250 mL of irrigation fluid (range 100 to 500 mL) during surgery that lasted approximately 7 to 8 minutes (range 0 to 42 minutes). In the Phase 2 trial, 57 patients received Omidira and 56 placebo.

In these studies, approximately 60% were female, the mean age was approximately 67 years (range 23-92 years) and approximately 80% were Caucasian.

There was one death in Study OMS302-ILR-003. Subject 193009, a 61 year old male died as a result of electrocution while working in an (b) (6). He underwent ILR for cataract on 12/13/11; he received OMS302. No patients discontinued study drug; the drug was administered in irrigation solution during cataract surgery and lens replacement.

Adverse events were reported in approximately 50% to 80% of patients and the majority were related to the surgical procedure (pain, inflammation), as shown in the table below.
The most common adverse events were eye pain, eye inflammation, anterior chamber inflammation, headache, and increased IOP. These events generally occurred at similar rates between treatment groups and are seen in associated with cataract surgery.

Common Treatment-Emergent Adverse Events with Subject Incidence of ≥ 2% in any OMS302 arm

	C09-001		OMS302-ILR-003		OMS302-ILR-004	
	Vehicle	OMS302	Placebo	OMS302	Placebo	OMS302
	(N=57)	(N=56)	(N=201)	(N=201)	(N=204)	(N=202)
Any Event	**45 (78.9%)**	**47 (83.9%)**	**150 (74.6%)**	**152 (75.6%)**	**128 (62.7%)**	**102 (50.5%)**
Eye Pain	16 (28.1%)	17 (30.4%)	86 (42.8%)	88 (43.8%)	76 (37.3%)	34 (16.8%)
Eye Inflammation	5 (8.8%)	11 (19.6%)	58 (28.9%)	60 (29.9%)	4 (2.0%)	3 (1.5%)
Headache	5 (8.8%)	4 (7.1%)	14 (7.0%)	5 (2.5%)	24 (11.8%)	21 (10.4%)
Anterior Chamber Inflammation	1 (1.8%)	1 (1.8%)	21 (10.4%)	19 (9.5%)	13 (6.4%)	17 (8.4%)
Ocular Discomfort	5 (8.8%)	1 (1.8%)	6 (3.0%)	2 (1.0%)	15 (7.4%)	10 (5.0%)
Photophobia	1 (1.8%)	4 (7.1%)	7 (3.5%)	8 (4.0%)	13 (6.4%)	4 (2.0%)
Intraocular Pressure Increased	1 (1.8%)	1 (1.8%)	10 (5.0%)	7 (3.5%)	4 (2.0%)	12 (5.9%)
Posterior Capsule Opacification	1 (1.8%)	0	1 (0.5%)	1 (0.5%)	14 (6.9%)	17 (8.4%)
Corneal Oedema	1 (1.8%)	0	5 (2.5%)	7 (3.5%)	7 (3.4%)	4 (2.0%)
Foreign Boday Sensation in Eyes	1 (1.8%)	0	0	1 (0.5%)	10 (4.9%)	7 (3.5%)
Vision Blurred	0	0	1 (0.5%)	0	16 (7.8%)	5 (2.5%)
Conjunctival Hyperaemia	3 (5.3%)	0	0	1 (0.5%)	10 (4.9%)	10 (5.0%)
Inflammation	13 (22.8%)	11 (19.6%)	0	0	0	0
Pain	11 (19.3%)	9 (16.1%)	0	0	3 (1.5%)	1 (0.5%)
Iritis	0	3 (5.4%)	0	0	3 (1.5%)	2 (1.0%)
Eye Irritation	0	0	2 (1.0%)	5 (2.5%)	4 (2.0%)	4 (2.0%)
Conjunctivitis	0	0	4 (2.0%)	6 (3.0%)	0	2 (1.0%)
Back Pain	0	1 (1.8%)	0	1 (0.5%)	3 (1.5%)	4 (2.0%)
Corneal Disorder	0	0	4 (2.0%)	3 (1.5%)	2 (1.0%)	0
Dry Eye	2 (3.5%)	1 (1.8%)	2 (1.0%)	1 (0.5%)	3 (1.5%)	0
Nausea	0	2 (3.6%)	1 (0.5%)	1 (0.5%)	0	5 (2.5%)
Cystoid Macular Oedema	0	2 (3.6%)	0	1 (0.5%)	0	1 (0.5%)
Anterior Chamber Cell	3 (5.3%)	1 (1.8%)	0	0	0	0

Arthritis	1 (1.8%)	2 (3.6%)	0	0	0	0

Source: Table 12 of the applicant's Integrated Summary of Safety (ISS).
Source – Statistical Review

Table 1: Any Treatment-Related Adverse Events with Subject Incidence of ≥ 1% in any OMS302 arm

	C09-001		OMS302-ILR-003		OMS302-ILR-004	
	Vehicle	OMS302	Placebo	OMS302	Placebo	OMS302
	(N=57)	(N=56)	(N=201)	(N=201)	(N=204)	(N=202)
Eye Disorders						
Anterior Chamber Inflammation	0	0	13 (6.5%)	8 (4.0%)	8 (3.9%)	10 (5.0%)
Conjunctival Hyperaemia	0	0	0	0	8 (3.9%)	10 (5.0%)
Corneal Oedema	0	0	1 (0.5%)	4 (2.0%)	3 (1.5%)	2 (1.0%)
Eye Inflammation	0	0	4 (2.0%)	2 (1.0%)	1 (0.5%)	0
Eye Pain	2 (3.5%)	5 (8.9%)	16 (8.0%)	11 (5.5%)	14 (6.9%)	6 (3.0%)
Foreign Body Sensation in Eyes	0	0	0	0	3 (1.5%)	1 (0.5%)
Ocular Discomfort	0	0	2 (1.0%)	1 (0.5%)	5 (2.5%)	3 (1.5%)
Photophobia	1 (1.8%)	1 (1.8%)	6 (3.0%)	4 (2.0%)	8 (3.9%)	3 (1.5%)
General Disorders and Administration Site Conditions						
Inflammation	3 (5.3%)	6 (10.7%)	0	0	0	0
Pain	1 (1.8%)	1 (1.8%)	0	0	0	0
Nervous System Disorders						
Headache	0	0	2 (1.0%)	0	2 (1.0%)	1 (0.5%)

Source: Table 6 of the applicant's ISS.
Source: Statistical Review

Ocular Adverse Reactions Reported by ≥ 2% of Subjects

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%)

Labeling will also reflect that systemic overdosage of phenylephrine may cause a rise in blood pressure. It may also cause headache, anxiety, nausea, vomiting, and ventricular arrhythmias.

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other non-steroidal anti-inflammatories (NSAIDs). The labeling will state that 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.

Comment:
I concur with the conclusions and recommendations for approval of the application by the clinical and statistical reviewers. The labeling has been revised and includes relevant safety information.

9. Advisory Committee Meeting

The application did not identify scientific issues for presentation and discussion at the Advisory Committee meeting.

10. Pediatrics

The application was presented at Pediatric Review Committee (PeRC) on September 11, 2013 and the committee agreed with the initial pediatric study plan. A written request letter was issued to the sponsor under IND 78,227 on October 3, 2013, for a clinical trial in 60 patients between the ages of 0 to 3 years with childhood cataracts. (b) (4)

11. Other Relevant Regulatory Issues

11.1 Office of Compliance Facility Inspections

Manufacturing facilities are acceptable, EES 5/30/2014.

11.2 Office of Scientific Investigation (OSI) Audits

Inspections of three investigators were completed and were classified as VAI; their data are considered adequate to support the application.

11.3 Debarment certification

Omeros Corporation in accordance with the Generic Drug Enforcement Act of 1992 hereby certify that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with NDA 205388.

11.4 Financial Disclosure

One investigator (b) (6) received payments with a cumulative value of around $30,000 for consulting services provided to Omeros' ophthalmic clinical program. He was an investigator in both Phase 3 studies and enrolled (b) (4) of the 821 subjects (b) (4) that participated in these trials. See clinical reviews for further details. The disclosed financial arrangements do not affect the approvability of the application.

11.5 Other Regulatory Issues

This is a 505(b)(2) application – the 505(b)(2) assessment committee has cleared this application from their perspective.

12. Labeling

- The proprietary name Omidria was found acceptable and the applicant notified via letter on 2/19/2014.
- Physician labeling (PLR) has been finalized and input from the reviewers and consultants was discussed and incorporated as appropriate.
- Carton and immediate container labels have been finalized after input from reviewers and consultants was discussed and changes incorporated as warranted
- Patient labeling/Medication guide – these are not proposed for the current product

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

NDA 205388 will be approved. All disciplines recommend approval, labeling has been finalized and manufacturing facilities are acceptable.

- Risk Benefit Assessment

During cataract surgery, when the contents of the lens are removed and a synthetic intraocular lens is inserted into the remaining lens capsule, the surgical procedure is simpler and safer if the surgeon has good access to the lens. This is best achieved if the pupil is dilated before the procedure to a diameter of at least 5 to 6 mm, and maintained until the procedure is completed. The duration of the procedure is generally in the range of 10-20 minutes but can be somewhat shorter or somewhat longer in duration.

There are a number of topical products that can be used to dilate the pupil and also for post-operative pain, these are summarized in the clinical reviews.

The current product is a combination of an alpha-1 adrenergic product, phenylephrine, and a NSAID, ketorolac. The combination product is for maintaining pupil size by preventing intraoperative miosis and reducing postoperative ocular pain. The product must first be diluted (4 mL Omidria in 500 mL of ophthalmic irrigating solution) and then is used during the procedure as needed.

This continuous irrigation continually replaces the solution and is expected to limit systemic absorption of the two ingredients. As shown in the PK substudy, most patients had low or undetectable levels.

The efficacy of the combination was superior to the efficacy of the individual components in a full factorial study. The efficacy was superior for both endpoints in two trials comparing Omidria to placebo for the endpoints of pupil size for the duration of the procedure and for lower rates of pain over a 10-12 hour period on the first day.

The product was used intraoperatively only. The most frequently observed AEs overall were eye pain, anterior chamber inflammation, headache, and increased IOP, all anticipated events following cataract or intraocular lens replacement surgery.

Overall, the benefits outweigh the risks when Omidria is used during cataract surgery or intraocular lens replacement.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

None

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RENATA ALBRECHT
05/30/2014