CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205388Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review for NDA 205388

Date	May 16, 2014
From	William M. Boyd, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #	205388
Applicant	Omeros Corporation
Date of Submission	7/30/13
PDUFA Goal Date	5/30/14
Type of Application	505(b)(2)
Name	Omidria
Dosage forms / Strength	phenylephrine and ketorolac injection, 1%/0.3%
Applicant's Proposed Indication(s)	For maintaining pupil size by preventing intraoperative miosis and for reducing postoperative pain
Recommended:	Recommended for Approval

1. Introduction

Omidria is a fixed-dose combination product containing phenylephrine hydrochloride (PE), an α_1-adrenergic receptor agonist, and ketorolac tromethamine (KE), a non-selective cyclooxygenase (COX) COX-1/COX-2 inhibitor. Omidria is added to standard irrigation solutions used during cataract surgery.

The component drug substances in Omidria have been used individually for many years. Phenylephrine, 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. OMS302 is the first drug product containing both agents.

Omidria is intended for admixture with sterile ophthalmic irrigating solutions. The finished dosage form contains 61 mM (12.37 mg/mL) phenylephrine HCl and 11 mM (4.24 mg/mL) ketorolac tromethamine, formulated in a (b) (4) sodium citrate (b) (4) (pH 6.3 (b) (4)). Each vial is filled to allow withdrawal of 4.0 mL of formulation concentrate for admixture with 500 mL of irrigation solution.

During surgical procedures, the admixed irrigation solution is administered either through a phacoemulsification surgical solution tubing set or via plastic syringe and needle. The intracameral space and to a lesser extent the surface of the eye are exposed to the irrigation admixture. This form of administration is expected to limit systemic absorption to only a small portion of the total drug substances present in a single dose of OMS302.

Throughout this review, Omidria may be alternately referred to as OMS302.

2. Background

This is a 505(b)(2) application.

Prior Approval/Availability of Proposed Active Ingredients 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- NDA 11663: Cyclomydril (cyclopentolate hydrochloride and phenylephrine hydrochloride) Ophthalmic Solution (withdrawn FR Effective 04/30/1984).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 (ketorolac ophthalmic solution)
- ANDA 75222: Ketorolac injection.

3. CMC

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT:

Composition of Drug Product

Component	Function	Amount per Vial (mg/4.0 mL)	Concentration Solution (mg/mL)	Concentration Admixed Solution^ (mg/mL)
Phenylephrine HCl, USP	Drug Substance	49.5	12.37 (61 mM)	0.0982
Phenylephrine (free base)	active			
Ketorolac Tromethamine, USP	Drug Substance	17.0	4.24 (11 mM)	0.0337
Ketorolac (free acid)	active			
Citric Acid Monohydrate, USP, Ph. Eur.*	(b) (4)	(b) (4)		
Sodium Citrate Dihydrate, USP, Ph. Eur.*				
Water for Injection, USP, Ph. Eur.				
Sodium Hydroxide, NF, Ph. Eur. (1 N)				(b) (4)
Hydrochloric Acid, NF, Ph. Eur. (1 N)				
(b) (4)				

(b) (4) sodium citrate (b) (4)
Target fill volume (b) (4) overfill to allow withdrawal of 4.0 mL of formulation concentration.
^After 4 mL of product diluted in 500 mL of BSS irrigation solution.

The OMS302 drug product is contained in a 5 mL Type 1 [redacted] (b) (4) clear glass vial. The container closure is an elastomeric stopper [redacted] (b) (4) The container closure is retained by an [redacted] (b) (4) seal and [redacted] (b) (4) flip-off cap. The drug product must be protected from ambient light and is therefore packaged for storage in a paper board container system.

PROPOSED SPECIFICATIONS:

Table 1: Regulatory Specification for OMS302

Attribute	Analysis Method	Acceptance Criteria
Description		
Color	Visual	Colorless
Appearance	Visual	Clear solution essentially free of visible particulate matter
Tests for Injections		
Volume	USP <1>, Ph. Eur. 2.9.17	NLT Labeled Volume of 4.0 mL
Subvisible Particulate Matter	[redacted] (b) (4)	[redacted] (b) (4)
Identity		
Spectra	HPLC/UV Method 1 (diode array)	UV Spectral Scan of Each Active Ingredient Matches UV Spectral Scan of Reference Standard with Corresponding Retention Time Over Range of [redacted] (b) (4) nm
Assay		
Phenylephrine HCl		
Potency	HPLC/UV Method 1	92.0% - 108.0% of Label Claim of 12.37 mg/mL
Ketorolac Tromethamine		
Potency	HPLC/UV Method 1	92.0% - 108.0% of Label Claim of 4.24 mg/mL
Impurities		
Degradation Products	HPLC/UV Method 1	*Specified (% weight / weight):* [redacted] (b) (4)

Table 1: Regulatory Specification for OMS302, continued

Attribute	Analysis Method	Acceptance Criteria
Physicochemical Tests		
pH of Solution	(b) (4)	(b) (4)
Osmolality		(b) (4) mOsm/kg to (b) (4) mOsm/kg
Biological Tests		
Sterility		Meets Requirements
Container Closure Integrity [b]		NMT (b) (4) standard cubic centimeters/second
Bacterial Endotoxins		NMT (b) (4) EU/mL or (b) IU/mL

a. Specification limit for particles (b) (4) µm applies only if light obscuration method fails and microscopic method is utilized.
b. Container closure integrity testing is only conducted during stability monitoring in lieu of sterility testing.

USP = United States Pharmacopeia Ph. Eur. = European Pharmacopoeia NLT = not less than NMT = not more than
HPLC = high performance liquid chromatography UV = ultraviolet spectroscopy
mOsm/kg = milliosmole/kilogram EU or IU = endotoxin unit

The specification limit for particulate matter is not consistent with many other ophthalmic products. (b) (4) limit should apply to either the light obscuration method or the microscopic method.

From the CMC Review finalized 4/22/2014:

The product is manufactured at a contract manufacturing facility (b) (4) via a relatively straightforward process (b) (4). The latter two operations have been reviewed by the New Drug Microbiology Staff. Sterility assurance has been evaluated from the Product Quality Microbiology perspective and found adequate.

The drug product specification provides 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. Based on discussions with the Pharm/Tox review team, and a comparison to related products, and on the available, albeit limited, release and stability data, it was determined that tighter acceptance criteria for individual specified and unspecified degradants, and total degradants were warranted. The applicant has tightened the acceptance criteria accordingly.

Phenylephrine HCl is manufactured by (b) (4). The chemistry, manufacturing and controls of the drug substance are documented in Type II DMF (b) (4)

Ketorolac tromethamine is manufactured by [redacted] (b) (4). The chemistry, manufacture and controls of the drug substance are documented in Type II DMF [redacted] (b) (4).

FACILITIES INSPECTIONS:

Office of Compliance evaluations of the phenylephrine drug substance manufacturing facility and of the drug product facility are pending as of the date of this review.

4. Nonclinical Pharmacology/Toxicology

From the Pharmacology/Toxicology Review finalized 4/21/2014:

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.

In addition, the existent nonclinical and clinical pharmacokinetic data support that the systemic exposure of phenylephrine and ketorolac at the intended dosing regimen is not expected to be above the range of values already observed after ocular and/or oral administration of FDA approved products.

5. Clinical Pharmacology/Biopharmaceutics

From the original Clinical Pharmacology Review finalized 4/22/2014:

[In the original submission], OMS302 (PE 12.37 mg/mL and KE 4.24 mg/mL) is proposed for

(b) (4) prevention of intraoperative miosis and reduction of (b) (4) post-operative ocular pain for intraocular lens replacement. The proposed dosage and route of administration for OMS302 for this indication is as follows: 4.0 mL of OMS302, PE 12.37 mg/mL and KE 4.24 mg/mL, is diluted in 500 mL of standard irrigation solution (e.g., balanced salt 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). The final irrigation solution is used during the procedure.

The current application presents data from four clinical studies to support the proposed indication of OMS302. These studies include one Phase 1/2 exploratory study designed to evaluate safety and potential efficacy endpoints (Study C07-005), one full-factorial study designed to evaluate the separate contributions of PE and KE to the proposed indication (Study C09-001), and two confirmatory Phase 3 safety and efficacy studies (Studies OMS302-ILR-003 and OMS302-ILR-004). One of the Phase 3 studies (OMS302-ILR-004) includes a pharmacokinetics (PK) substudy.

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.

In Study OMS302-ILR-004, 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.

(b) (4) KE did not display any treatment effect in inhibiting miosis compared to placebo in Study C09-001 (p=1.0), and any additive effect on PE in pupil diameter changes when KE was administered in combination with PE in both Study C07-005 (p=1.0) and Study C09-001 (p=1.0).

In Study C07-005, KE 60 µM (final concentration) did not provide clinical meaningful effects in the ocular Pain Score. KE at 89 µM also displayed contribution to the treatment effect in the ocular Pain Score when KE was administered with PE (p=0.0093) in Study C09-001. The justification of the dose selection (i.e., KE 89µM) is acceptable.

PE at 483 µM displayed slightly higher AUCs of reduced pupil diameter compared to placebo group in Study C07-005 (p=0.4) and in Study C09-001 (p=0.7). A slight contribution to the treatment effect in the change in pupil diameter was demonstrated when PE was administered in combination with KE in Study C09-001 (p=0.7). Although it was not statistically significant, the

contribution of PE at 483 µM to the treatment effect is considered to be acceptable, since the baseline in pupil diameter includes pre-operative mydriatic treatment.

The administration of topical KE ophthalmic solution before the evaluation of efficacy endpoints at 24-hour time point may change the results of the efficacy analysis in any of the clinical studies.

6. Sterility Assurance

The drug product is a sterile parenteral solution; therefore, the integrity of the seal generated between the glass vial container and elastomeric closure, as it relates to preventing microbial contamination has been evaluated by performing container closure integrity studies.

Acceptance criteria and results of the studies are summarized below.

Table 2: (b) (4) Container Closure Integrity Study Results

Acceptance Criteria	Study Results
Microbial Ingress: (b) (4)	500 test units: no growth 10 positive controls: 9 positive controls exhibit growth 2 negative controls: growth in both containers
Peracetic acid Sterilization Challenge: (b) (4)	2 test units inoculated with Bacillus subtilus: growth 2 test units inoculated with Pseudomonas aeruginosa: growth 2 test units inoculated with Aspergillus niger: growth 2 test units inoculated with Candida albicans: growth 2 test units inoculated with Staphylococcus epidermidis: growth 2 test units inoculated with Corynebacterium species: growth 2 test units inoculated with Acinetobacter iwoffii: growth 2 positive controls inoculated with Bacillus subtilus: growth 2 positive controls inoculated with Pseudomonas aeruginosa: growth 2 positive controls inoculated with Aspergillus niger: growth 2 positive controls inoculated with Candida albicans: growth 2 positive controls inoculated with Staphylococcus epidermidis: growth 2 positive controls inoculated with Corynebacterium species: growth 2 positive controls inoculated with Acinetobacter iwoffii: growth 2 negative controls exposed to sterilization cycle: no growth 2 negative controls not exposed to sterilization cycle: no growth

7. Clinical/Statistical - Efficacy

From the original Medical Officer Review dated 5/9/2014:

Study	Phase	Study Design	Test Product	Number of Subjects
OMS302-ILR-004	Phase 3	Randomized, parallel group, double-masked, placebo controlled study	OMS302 (483 µM PE and 89 µM KE) or Placebo diluted in BSS Single dose, intraocular irrigation and intracameral perfusion	416 total: 209 OMS302 207 Placebo PK subset: 26 total 14 OMS302 12 Placebo
OMS302-ILR-003	Phase 3	Randomized, parallel group, double-masked, placebo controlled study	OMS302 (483 µM PE and 89 µM KE) or Placebo diluted in BSS Single dose, intraocular irrigation and intracameral perfusion	405 total: 203 OMS302 202 Placebo
C09-001	Phase 2	Randomized, parallel group, double-masked, vehicle controlled study	PE and KE alone and in combination (OMS302), diluted in BSS Four arms: (1) 483 µM PE (2) 89 µM KE (3) 483 µM PE and 89 µM KE (4)Vehicle control Single dose, intraocular irrigation and intracameral perfusion	223 total: 56 OMS302 56 PE 55 KE 56 Vehicle
C07-005	Phase 1/Phase 2	Randomized, controlled, double-masked, vehicle- and phenylephrine HCl-controlled	PE and KE alone and in combination (OMS302), diluted in BSS; Three arms: (1) 483 µM PE (2) 483 µM PE and 60 µM KE (3) BSS Vehicle Single dose, intraocular irrigation and intracameral perfusion	61

Study OMS302-ILR-003 and Study OMS302-ILR-004

Study OMS302-ILR-003: Mean Area Under the Curve (AUC) Analysis of Change From Baseline in Pupil Diameter (mm) During Surgery (Full Analysis Set Population)

	Placebo N=201	**OMS302 N=201**
Mean AUC		
Number of Patients With Video Data	180	184
Mean (sd)	-0.5 (.58)	0.1 (.41)
Min, Max	-2.9, 2.1	-2.7, 1.3
Difference in Mean AUC		
CMH Weighted Mean Difference (SE)	0.577 (0.052)	
95% CI	0.475, 0.678	
P-Value	<.0001	

Study OMS302-ILR-004: Mean Area Under the Curve (AUC) Analysis of Change From Baseline in Pupil Diameter (mm) During Surgery (Full Analysis Set Population)

	Placebo N=204	**OMS302 N=202**
Mean AUC		
Number of Patients With Video Data	200	195
Mean (sd)	-0.5 (.57)	0.1 (.43)
Min, Max	-2.3, 1.5	-2.2, 2.3
Difference in Mean AUC		
CMH Weighted Mean Difference (SE)	0.590 (0.049)	
95% CI	0.494, 0.686	
P-Value	<.0001	

Study OMS302-ILR-003: Supportive Analysis of Pupil Diameter (mm) During Surgery (Full Analysis Set Population)

	Placebo N=201	**OMS302 N=201**
Subjects With >=6mm At Cortical Clean-up In Subjects With Video Data	139/180 (77.2%)	177/184 (96.2%)
P value		<0.0001
Pupil Diameter (mm) at cortical Clean-up		
N	180	184
Mean (sd)	7.1 (2.0)	8.0 (1.8)
Min, Max	3.8, 18.0	2.7, 17.8
P value		<0.0001

	Placebo N=201	**OMS302 N=201**
Subjects With Degree of Pupillary Constriction		
<0.5mm	9	78
>=0.5 to <1.0mm	24	70
>=1.0 to <1.5mm	41	11
>=1.5 to <2.0mm	36	9
>=2.0 to <2.5mm	20	10
>=2.5mm	50	6
P value		<0.0001

Study OMS302-ILR-004: Supportive Analysis of Pupil Diameter (mm) During Surgery (Full Analysis Set Population)

	Placebo N=204	**OMS302 N=202**
Subjects With >=6mm At Cortical Clean-up In Subjects With Video Data	154/200 (77.0%)	187/195 (95.9%)
P value		<0.0001
Pupil Diameter (mm) at cortical Clean-up		
N	200	195
Mean (sd)	7.5 (2.5)	8.6 (2.4)
Min, Max	3.3, 18.7	4.8, 19.2
P value		<0.0001
Subjects With Degree of Pupillary Constriction		
<0.5mm	14	92
>=0.5 to <1.0mm	29	58
>=1.0 to <1.5mm	47	26
>=1.5 to <2.0mm	40	13
>=2.0 to <2.5mm	17	4
>=2.5mm	53	2
P value		<0.0001

Both studies met the primary endpoint of mydriasis (i.e., 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 intraocular lens replacement and measured from the video capture by a masked central reader) with statistical significance.

Study OMS302-ILR-003: Mean Area Under the Curve (AUC) Analysis of Ocular Pain VAS Score Within 12 Hours Post-operatively (Full analysis Set Population)

	Placebo N=201	**OMS302 N=201**
Mean AUC		
Mean (sd)	9.2 (12.9)	4.1 (8.1)
Min, Max	0.0, 65.3	0.0, 66.9
Difference in Mean AUC		
CMH Weighted Mean Difference (SE)	-5.199 (1.076)	
95% CI	-7.307, -3.091	
P-Value	<.0001	

Study OMS302-ILR-004: Mean Area Under the Curve (AUC) Analysis of Ocular Pain VAS Score Within 12 Hours Post-operatively (Full analysis Set Population)

	Placebo N=204	**OMS302 N=202**
Mean AUC		
Mean (sd)	8.9 (15.2)	4.3 (8.8)
Min, Max	0.0, 85.8	0.0, 58.4
Difference in Mean AUC		
CMH Weighted Mean Difference (SE)	-4.580 (1.192)	
95% CI	-6.917, -2.244	
P-Value	0.0002	

Study OMS302-ILR-003: Ocular Pain VAS Score During 12 Hours Post-operatively (Full Analysis Set Population)

	Placebo N=201	**OMS302 N=201**
Subjects With Pain Free (VAS=0) At all Timepoints	28	48
P value		0.0108
Subjects with Maximum VAS Score During 12 Hours Post-operatively		
>=0 to <=5	97	137
>5 to <=10	23	13
>10 to <=15	9	14
>15 to <=20	11	7
>20	61	30
P value		0.0002
Subjects with Moderate to Severe Pain (VAS >=40) At Any Timepoint	30	13
P value		0.0061

Study OMS302-ILR-004: Ocular Pain VAS Score During 12 Hours Post-operatively (Full Analysis Set Population)

	Placebo N=204	**OMS302 N=202**
Subjects With Pain Free (VAS=0) At all Timepoints	41	56
P value		0.0806
Subjects with Maximum VAS Score During 12 Hours Post-operatively		
>=0 to <=5	101	126
>5 to <=10	21	20
>10 to <=15	19	14
>15 to <=20	10	10
>20	51	32
P value		0.0959
Subjects with Moderate to Severe Pain (VAS >=40) At Any Timepoint	27	16
P value		0.0760

Pain during the initial 10-12 hours postoperatively was significantly less in the Omidria-treated groups than in the placebo-treated groups in both studies.

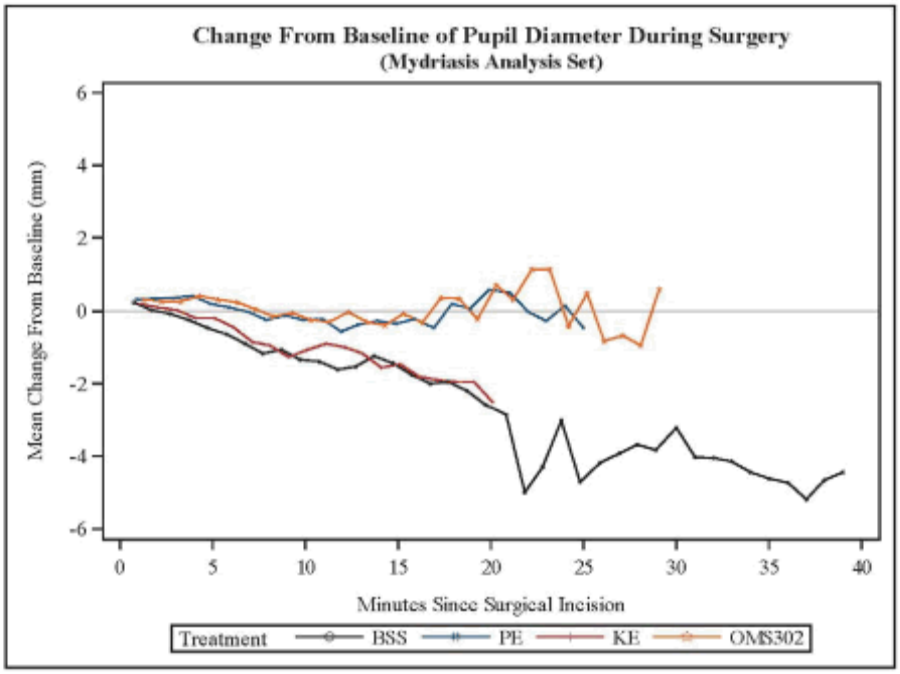
Study C09-001 (full factorial)
The primary efficacy endpoints of this study were:

- Change in pupil diameter (mydriasis) as determined by video capture during cataract extraction with lens replacement (CELR) using the change over time from surgical baseline (immediately prior to surgical incision) to the end of the surgical procedure (wound closure).

- Post-operative ocular pain as measured by the visual analog scale (VAS) at 2, 4, 6, 8, and 10–12 hours after CELR surgery.

Video recordings of each subject's surgical procedure were used to measure the pupil diameter over time. A masked central reader performed the pupil size measurements. Post-operative ocular pain was reported in a subject diary using the VAS at approximately 2 hours, 4 hours, 6 hours, 8 hours, and 10–12 hours post-surgery.

Figure 3: Intraoperative Change in Pupil Diameter (Mydriasis Analysis Set)

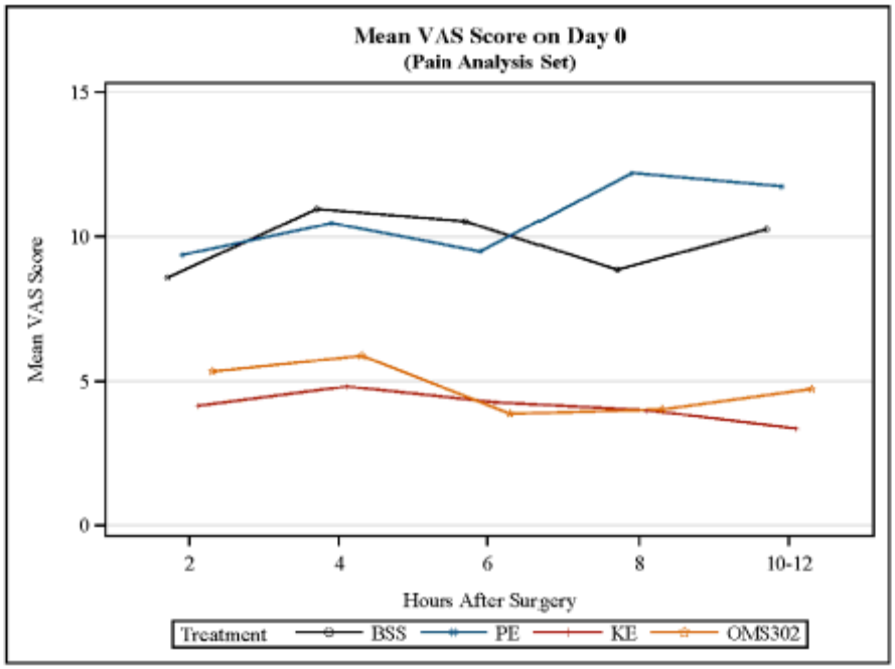


Study C09-001: Repeated Measures Analysis of Change from Baseline in Pupil Diameter (mm) During Surgery (Mydriasis Analysis Set)

	OMS302-Vehicle	OMS302-KE
Least squares mean difference (SE)	0.9 (0.1)	0.7 (0.1)
95% CI	0.6, 1.1	0.5, 0.9
P-Value	0.0001	0.0001

Pupil diameter decreased throughout the surgical procedure in both the vehicle and KE groups, but mydriasis was consistently maintained in both the PE and OMS302 groups. The superiority of OMS302 over vehicle and KE demonstrates the contribution of PE to maintenance of mydriasis.

Figure 4: Postoperative Ocular Pain VAS Score (Pain Analysis Set)



Study C09-001: Repeated Measures Analysis of Ocular Pain VAS Score within 12 Hours Post-Operatively (Pain Analysis Set)

	OMS302-Vehicle	OMS302-KE
Least squares mean difference (SE)	-4.5 (2.2)	-5.9 (2.2)
95% CI	-8.9, -0.2	-10.3, -1.5
P-Value	0.0001	0.0001

Pain score in vehicle and PE groups were consistently higher than in the OMS302 and KE groups. The superiority of OMS302 over PE and vehicle demonstrates the contribution of KE to the reduction of post-operative ocular pain.

Additional Analyses - Analysis of Patients with Distorted Video Images

In the images in which the microscope is not above the eye, … If the ruler is parallel to the long axis of the iris, each is measured on the same scale and there is no distortion of the iris measurements. If the ruler is not parallel to the long axis, the ruler is foreshortened compared to the long axis of the iris and the iris diameter is artificially increased due to the angle of the observation. The relative measures of the pupil and iris are not affected when measured during the surgical procedure, but the absolute measures are artificially increased and may result in pupil diameters out of physically plausible range.

Per the applicant, a physician reviewed all images of ruler capture and identified 19 subject videos (11 placebo and 8 OMS302) in Study OMS302-ILR-003 and 48 subject videos (23 placebo and 25 OMS302) in Study OMS302-ILR-004 that were recorded at an angle that was not above the study eye and in which the ruler was not measured parallel to the long axis of the iris that were recorded at an angle that was not above the study eye and in which the ruler was not measured parallel to the long axis of the iris.

Study OMS302-ILR-003: Comparison of Results of Pupil Diameter Analyses of the Full Analysis Set (FAS) With and Without Subjects With Distorted Video Images

	All FAS N=184	**FAS Without Distorted Images N=176**
Mean AUC Change From Baseline		
CMH Weighted Mean Difference	0.577	0.540
P Value	<0.0001	<0.0001
Difference in Incidence of Subjects With Pupil diameter <6mm at Cortical Cleanup	19.0%	19.7%
P-value	<0.0001	<0.0001

Study OMS302-ILR-004: Comparison of Results of Pupil Diameter Analyses of the Full Analysis Set (FAS) With and Without Subjects With Distorted Video Images

	All FAS N=395	**FAS Without Distorted Images N=347**
Mean AUC Change From Baseline		
CMH Weighted Mean Difference	0.59	0.56
P Value	<0.0001	<0.0001
Difference in Incidence of Subjects With Pupil diameter <6mm at Cortical Cleanup	19.1%	21.3%
P-value	<0.0001	<0.0001

Exclusion of subjects due to positional distortion of video images of certain subjects did not alter the treatment effect observed in either study.

Efficacy Summary Statement

Multiple adequate and well controlled studies demonstrate the efficacy of Omidria (phenylephrine and ketorolac injection) 1%/0.3% in producing clinically significant mydriasis and reduced postoperative pain compared to vehicle.

8. Safety

From the original Medical Officer Review dated 5/9/2014:

Two clinical studies (OMS302-ILR-003 and OMS302-ILR-004) were used to evaluate safety. Between the 2 studies there were 403 patients in the safety database who received OMS302.

Study OMS202-ILR-003: Extent of Exposure

	Placebo N=201	**OMS302 N=201**
Total Volume of Study Irrigation solution (mL)		
Mean (sd)	252.2 (61.7)	248.0 (56.6)
Min, Max	125, 497	150, 470
Study Drug Administration Duration (minutes)		
Mean (sd)	7.7 (4.5)	7.6 (5.0)
Min, Max	1, 35	0, 42

Study OMS202-ILR-004: Extent of Exposure

	Placebo N=204	**OMS302 N=202**
Total Volume of Study Irrigation solution (mL)		
Mean (sd)	255.8 (70.7)	254.3 (63.4)
Min, Max	125, 500	100, 500
Study Drug Administration Duration (minutes)		
Mean (sd)	7.7 (5.1)	7.3 (4.1)
Min, Max	1, 39	1, 29

Adverse Events

Study OMS302-ILR-003: Subject Incidence of Treatment-Emergent AEs by System Organ Class

System Organ Class	**Placebo N=201**	**OMS302 N=201**
Any Event	**154**	**156**
Eye disorders	**148**	**150**
Anterior chamber fibrin	0	1
AC inflammation	21	19
Conjunctival hemorrhage	3	1
Conjunctival hyperemia	0	1
Conjunctival edema	1	1
Conjunctivitis	4	6
Corneal disorder	4	3
Corneal edema	5	7
Corneal pigmentation	0	1
CME	0	1
Dry eye	2	1
Eye inflammation	58	60
Eye irritation	2	5
Eye pain	86	88
Eye pruritus	0	1
FBS in eyes	0	1
Macular degeneration	1	0
Macular hole	1	0
Ocular discomfort	6	2
Photophobia	7	8
PCO	1	1
SPK	2	3
Retinal hemorrhage	1	0
Trichiasis	0	1
Vision blurred	1	0
Visual Acuity reduced	1	1
Vitreous detachment	2	1
Vitreous floater	0	1
GI disorders	**2**	**2**
Abdominal discomfort	1	0
Dyspepsia	0	1
Nausea	1	1
Infections	**1**	**2**
Bronchitis	0	1
Hordeolum	0	1
Oral herpes	1	0

Injury, Poisoning, and Procedural Complications	**7**	**1**
Corneal abrasion	3	1
Exoriation	1	0
Facial bones fracture	1	0
Fall	2	0
Foreign body in eye	1	0
Laceration	1	0
Procedural hypertension	1	0
Wrist fracture	1	0
Investigations	**12**	**7**
Blood pressure increased	2	0
IOP increased	10	7
Musculoskeletal disorders	**2**	**6**
Arthralgia	2	2
Back pain	0	1
Musculoskeletal pain	0	1
Myalgia	0	1
Pain in extremity	0	1
Nervous system disorders	**15**	**5**
Head discomfort	1	0
Headache	14	5
Psychiatric disorders	**3**	**0**
Anxiety	1	0
Insomnia	2	0
Respiratory disorders	**1**	**2**
Nasal discomfort	0	1
Oropharyngeal pain	0	1
Rhinorrhea	1	0
Metabolism and nutrition disorders	**0**	**1**
DM	0	1
General disorders	**0**	**1**
Electrocution	0	1

Study OMS302-ILR-004: Subject Incidence of Treatment-Emergent AEs by System Organ Class

System Organ Class	Placebo N=204	OMS302 N=202
Eye disorders	**29**	**22**
Abnormal sensation in eye	1	0
AC inflammation	8	10
Conjunctival hemorrhage	1	0
Conjunctival hyperemia	8	10
Conjunctival edema	0	1
Corneal disorder	1	0
Corneal edema	3	2
Eye inflammation	1	0
Eye irritation	1	1
Eye pain	14	6
Eyelid pain	0	1
FBS in eyes	3	1
Glare	0	1
Iridocele	1	0
Iris disorder	1	0
Lacrimation increased	1	0
Miosis	1	0
Mydriasis	0	1
Ocular discomfort	5	3
Photophobia	8	3
Vision blurred	1	1
Vitreous floaters	0	1
GI disorders		
Nausea	0	1
Nervous system disorders		
Headache	2	1

The most frequently observed AEs overall were eye pain, eye inflammation, anterior chamber inflammation, headache, and increased IOP, all anticipated events following intraocular lens replacement (ILR) surgery. These events occurred at a similar incidence across the treatment groups.

Deaths

Study OMS302-ILR-003: One subject (Subject 193009) died during the study as a result of electrocution in an industrial accident. This was a 61 year old male who underwent ILR for cataract on 12/13/11. He was randomized to the OMS302-treatment group and received OMS302. On (b) (6), the subject was electrocuted and died while working on an (b) (6). The subject was not taking any concomitant medications and had no relevant medical history.

Study OMS302-ILR-004: No deaths.

Safety Summary Statement

The safety of Omidria (phenylephrine and ketorolac injection) 1%/0.3% in adults is supported by adequate and well controlled studies. The most frequently observed AEs overall were eye pain, eye inflammation, anterior chamber inflammation, headache, and increased IOP, all anticipated events following cataract or intraocular lens replacement (ILR) surgery

9. 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.

10. Pediatrics

Safety and effectiveness of Omidria in pediatric patients below the age of 18 years have not been established. Height and weight data were not collected as part of this protocol. This application was reviewed by the Pediatric Review Committee (PeRC) and on 10/30/13 and PeRC agreed with the deferral for all pediatric age groups.

A single pediatric study in at least 60 patients (30 per arm) undergoing cataract surgery is planned to be conducted in the U.S. (b) (4)

11. Other Relevant Regulatory Issues

Pharmacology/Toxicology, Clinical Pharmacology, Clinical, and Biostatistics have recommended approval of this new drug application. Office of Compliance evaluations of the

phenylephrine drug substance manufacturing facility and of the drug product facility are pending as of the date of this review.

FINANCIAL DISCLOSURE

(b) (6) received payments with a cumulative value of $30,004.39 for consulting services provided in relation to Omeros' ophthalmic clinical program (Study OMS302-ILR-003 and 004).

Study OMS302-ILR-003 was a double blind, placebo-controlled, multicenter, randomized trial. (b) (6) was 1 of 18 investigator sites participating in the trial. He was responsible for enrolling (b) (4) subjects out of a total of 405 subjects in the trial. The two co-primary endpoints in this study were objective measures, neither of which were directly evaluated or assessed by (b) (6) Change in pupil diameter over time from surgical baseline to the end of the surgical procedure which was evaluated by a masked central reader. Early post-operative pain which was obtained from a Visual Analog Scale completed by the subject.

Study OMS302-ILR-004 was a double blind, placebo-controlled, multicenter, randomized trial. (b) (6) was 1 of 16 investigator sites participating in the trial. He was responsible for enrolling only (b) (4) subject out of a total of 416 subjects in the trial. The two co-primary endpoints in this study were objective measures, neither of which were directly evaluated or assessed by (b) (6) 1) Change in pupil diameter over time from surgical baseline to the end of the surgical procedure which was evaluated by a masked central reader, and 2) Early post-operative pain which was obtained from a Visual Analog Scale completed by the subject.

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

OSI

An Office of Scientific Investigations (OSI) audit was requested. Per the Clinical Inspection Summary finalized 4/14/14:

The following studies were inspected in support of the indication:

Protocol C09-001, entitled A Study of Phenylephrine HCl's and Ketorolac Tromethamine's Ability, Alone and in Combination, to Maintain Mydriasis and Relieve Pain and Inflammation in Subjects Undergoing Unilateral Cataract Extraction with Lens Replacement (CELR)", and

Protocol OMS302-ILR-003, entitled "A Phase 3 Randomized, Double-Masked, Placebo-Controlled Study of the Effect of OMS302 on Intraoperative Pupil Diameter and early Postoperative Pain in Subjects Undergoing Intraocular Lens Replacement with Phacoemulsification", and

Protocol OMS302-ILR-004, entitled A Phase 3 Randomized, Double-Masked,

Placebo-Controlled Study of the Pharmacokinetics of OMS 302 on Intraoperative Pupil Diameter and Early postoperative pain in Subjects Undergoing Intraocular lens Replacement with Phacoemulsification".

The clinical sites of Drs. Dunn, Lim, and Marsico were selected for inspection because they were amongst the highest enrolling for their respective protocols.

Name of CI, Location	Protocol #/ Site #/ # of Subjects	Inspection Dates	Final Classification
Steven H. Dunn, MD Houston Eye Associates 915 Gessner, Suite 250 Professional Building #3 Houston, TX 77024	C09-001/ 190/ 43	15 Jan-5 Feb 2014	VAI
Steven H. Dunn, MD Houston Eye Associates 915 Gessner, Suite 250 Professional Building #3 Houston, TX 77024	OMS302-ILR-003/ 190/ 64	15 Jan-5 Feb 2014	VAI
Steven H. Dunn, MD Houston Eye Associates 915 Gessner, Suite 250 Professional Building #3 Houston, TX 77024	OMS302-ILR-004/ 190/ 80	15 Jan-5 Feb 2014	VAI
John M. Lim, MD Houston Eye Associates 915 Gessner, Suite 250 Professional Building #3 Houston, TX 77024	OMS302-ILR-003 195/ 68	17 Jan-4 Feb 2014	VAI
John M. Lim, MD Houston Eye Associates 915 Gessner, Suite 250 Professional Building #3 Houston, TX 77024	OMS302-ILR-004/ 195/ 62	17 Jan-4 Feb 2014	VAI
Nicholas P. Marsico, M.D. East West Eye Institute 420 E. 3rd St., Suite 603 Los Angeles, CA 90013	C09-001/ 198/ 32	15-22 Nov 2013	VAI

Key to Classifications
NAI = No deviation from regulations.
VAI = Deviation(s) from regulations.
OAI = Significant deviations from regulations. Data unreliable.
Pending = Preliminary classification based on information in Form FDA 483 or preliminary communication with the field; EIR has not been received from the field or complete review of EIR is pending.

Dr. Marsico was issued a Form FDA 483. The final classification of this inspection was Voluntary Action Indicated (VAI). Other than the consideration noted above; i.e., dispensation of

a corticosteroid to all subjects, the data generated by this clinical site and submitted by the applicant appear adequate in support of the respective indication.

Drs. Dunn and Lim were issued Form FDA 483s. The final classification of these inspections was Voluntary Action Indicated (VAI). The amount of test article withdrawn from the dispensing vials was not documented for C09-001 and/or OMS302-IL-003. This lack of documentation was acknowledged by both Drs. Dunn and Lim. Both investigators implemented corrective actions to capture this data for subsequent study activities. There appears to be sufficient documentation to assure that the drug was available to the site, that the protocol contained specific instructions for preparation of the test article, that study kits were documented as received and used, and that subjects were dispensed the test article. OSI considers the available documentation, in conjunction with the investigators' written responses, to provide reasonable assurance that subjects were treated in compliance with the protocol.

BIOSTATISTICS

Per the Biostatistics consultative review finalized 4/25/2014:

Study C09-001 was a full-factorial design study to evaluate the contribution of each component to the combination product. 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.

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

Studies OMS302-ILR-003 and OMS302-ILR-004 were similarly designed and each compared OMS302 with placebo. The two efficacy endpoints were the same as Study C09-001 except postoperative pain was a co-primary endpoint in Study OMS302-ILR-004; whereas it was the first secondary endpoint in a hierarchical chain 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.

There are no major statistical issues identified for any of three studies.

OMS302 is effective in maintaining pupil dilution during the intraocular lens replacement surgery compared to KE and placebo and in reducing ocular pain during the first 12 hours postoperatively compared to PE and placebo.

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

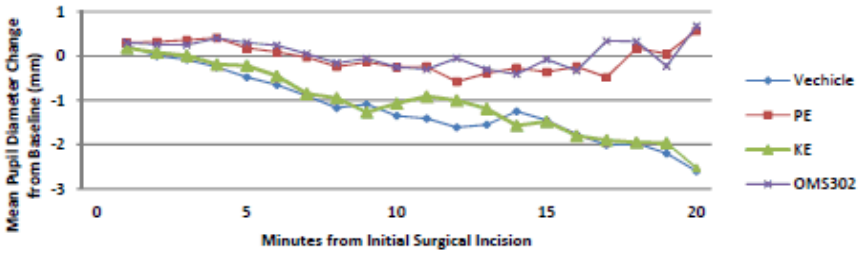


Figure 2: Study OMS302-ILR-003 Intraoperative Pupil Diameter (mm) Mean Change-from-Baseline

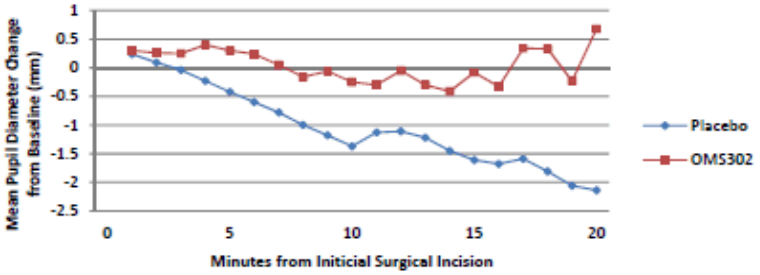
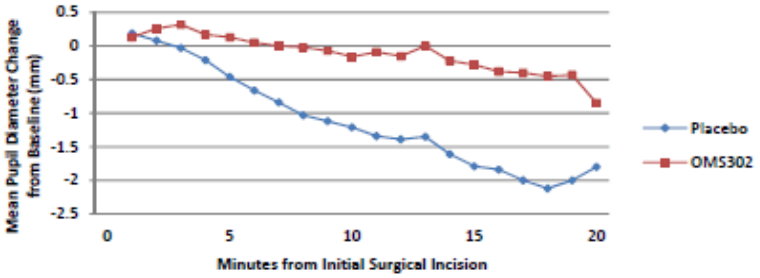


Figure 3: Study OMS302-ILR-004 Intraoperative Pupil Diameter (mm) Mean Change-from-Baseline



Source for figures: Table 39.

Table 1: Summary of Proportion of Patients with Zero VAS Scores Post-Surgery at Each Time Point for All Three Studies (All Treated Subjects)

	Study C09-001			Study OMS302-ILR-003			Study OMS302-ILR-004		
	OMS302	PE	Diff (95% CI)	OMS302	Placebo	Diff (95% CI)	OMS302	Placebo	Diff (95% CI)
2 Hours	31/55 (56.4%)	28/56 (50.0%)	6.4% (-12.2%, 24.9%)	81/201 (40.3%)	61/201 (30.4%)	9.9% (0.7%, 19.2%)	101/202 (50.0%)	75/203 (37.0%)	13.1% (3.5%, 22.6%)
4 hours	26/49 (53.1%)	20/52 (38.5%)	14.6% (-4.6%, 33.8%)	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	29/55 (52.7%)	22/55 (40.0%)	12.7% (-5.8%, 31.2%)	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	27/51 (52.9%)	18/54 (33.3%)	19.6% (1.0%, 38.2%)	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	30/54 (55.6%)	18/55 (32.7%)	22.8% (4.7%, 41.0%)	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 based on chi-square test
Source: statistical reviewer's analysis.

OPDP
A review of the substantially complete labeling was completed by the Office of Prescription Drug Promotion (OPDP) on 4/14/2014:

Comment [CGC2]: OPDP Comment: We are concerned that the term "prevention" suggests absolute efficacy for all patients on Omidria and at all timepoints. Figure 3 of the CLINICAL STUDIES section presents the intraoperative pupil diameter at 0, 5, 10, and 15 minutes from initial surgical incision. We note that a decrease in pupil diameter (approximately -0.5 mm) was shown in Omidria patients in both studies at various timepoints. Is this considered "preventing miosis?" If not, we recommend utilizing the [redacted] (b) (4)" language or simply communicating [redacted] (b) (4)"; however, we defer to DTOP. Please apply this comment to additional mentions of this indication (such as in the INDICATIONS AND USAGE and CLINICAL PHARMACOLOGY sections of the full PI).

DTOP Response: *The applicant has chosen to revise the indication at the Agency's request. The applicant wishes the dilation indication to read, "...maintains pupil size by preventing intraoperative miosis." This wording of this indication is supported by the individual pharmacology of the constituent drug components and the clinical trial results.*

Comment [CGC4]: OPDP Comment: We note that this language [(b) (4) postoperative pain] is not used in the INDICATIONS AND USAGE section of the full PI. We recommend revising so consistent language is used in the Highlights and the full PI.

DTOP Response: *The applicant has chosen to remove the word, (b) (4) " from the pain indication.*

Comment [CGC5]: OPDP Comment: We recommend listing these common adverse reactions in an order of decreasing incidence. For example, based on the incidence rates in Table 1, "eye inflammation, anterior chamber inflammation, intraocular pressure increased, posterior capsule opacification, eye irritation, and foreign body sensation in eyes."

DTOP Response: *The adverse reactions have been re-worded by the applicant to more accurately combine similar reactions; the events are all likely due to the surgery and not related to the use of the drug product. This is reflected in the similar incidence of these events between the test product group and the vehicle.*

Comment [CGC6]: OPDP Comment: Is Omidria indicated for use during any ophthalmic surgery or only during cataract surgery? If Omidria is indicated for different ocular surgeries, we recommend revising to "used during ocular surgery" or similar. If, however, Omidria is only indicated for use during cataract surgery we recommend specifying this in each respective indication [redacted] (b) (4) "reduction of ocular pain after cataract surgery). In the past, we have had issues with ophthalmic drug products promoting efficacy (such as resolution of pain) after any type of ocular surgery, when the drug

was only found to be safe and effective in patients undergoing cataract surgery. Please apply this comment to the applicable Highlights section as well.

DTOP Response: *Omidria is indicated for use during cataract surgery or intraocular lens replacement surgery.*

Comment [CGC8]: OPDP Comment: We note that other available phenylephrine ophthalmic products (2.5% and 10%) include additional warnings and precautions such as: cardiovascular reaction and rebound miosis. Similarly we note that other available ketorolac ophthalmic products (such as Acular) include additional warnings and precautions such as: delayed healing, increased bleeding time, and corneal effects We acknowledge that Omidria is diluted into ophthalmic irrigation solution and that it is only given while the patient is undergoing ocular surgery. We would just like to confirm that these risks are not associated with this product.

DTOP Response: *These risks are not associated with this product.*

Comment [CGC9]: OPDP Comment: We note that a phenylephrine ophthalmic label (NDA 203510) includes the following additional information, "The post-treatment blood pressure of patients with cardiac and endocrine diseases and any patients who develop symptoms should be carefully monitored." We acknowledge that the concentration of phenylephrine in Omidria is only 1% as opposed to 2.5% and 10% for the NDA 203510 product. Does this information apply to this phenylephrine containing product as well? If so, we recommend including.

DTOP Response: *This information does not apply to this phenylephrine-containing product.*

Comment [CGC10]: OPDP Comment: If possible, we recommend including additional study information including: dose(s) received and duration, demographics of the exposed population, and any pertinent exclusion criteria. We also recommend communicating the percentage of patients that discontinued treatment due to adverse reactions (if applicable) and identify which adverse reaction resulted in the most discontinuations. We reference the January 2006 Guidance for Industry: Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format.

DTOP Response: *This product is utilized during cataract surgery or intraocular lens replacement surgery. Patients cannot discontinue during the surgery.*

Comment [CGC11]: OPDP Comment: Would it be appropriate to include this information [The use of Omidria during late pregnancy should be avoided] in the Highlights section of this PI (under a USE IN SPECIFIC POPULATIONS header)?

DTOP Response: *For consistency with other ophthalmic NSAIDS, this language is retained in Section 8.1.*

Comment [CGC13]: OPDP Comment: We are concerned that this information [Ketorolac, by inhibiting prostaglandin synthesis secondary to ocular surgical insult or direct mechanical stimulation of the iris, also prevents surgically induced miosis]conflicts with data presented in Section 14 for the clinical study performed comparing Omidria to phenylephrine alone, ketorolac alone, and vehicle. Specifically, the Clinical Studies section states, (b) (4) Does Ketorolac maintain mydriasis/prevent miosis? If not, we recommend deleting this misleading information.

DTOP Response: *The language in Section* (b) (4) *has been revised.*

Comment [CGC14]: OPDP Comment: If possible we recommend communicating the dose patients received and the average duration that patients were exposed to Omidria. We also recommend communicating the demographics of patients evaluated in this study, if possible.

DTOP Response: *Omidria is administered via dilution into irrigating solution used during cataract surgery or intraocular lens replacement surgery. Dosing and average duration information is potentially misleading and never accurately known.*

Comment [CGC15]: OPDP Comment: We note that the pupil diameter efficacy data is presented for 0, 5, 10, and 15 minutes from the initial surgical incision. When was Omidria given in these studies? Was it at the time of initial incision as well or a certain time period before the first incision? Would it be appropriate to communicate when Omidria was given to the patients in these studies?

DTOP Response: *Omidria is administered via dilution into irrigating solution used continuously during cataract surgery or intraocular lens replacement surgery.*

Comment [CGC16]: OPDP Comment: It appears that the graph for Study 1 presents 2 additional data points outside the 15 minutes from initial surgical incision timepoint. Was the study designed to measure efficacy at timepoints outside the 15 minute timepoint? If not, we recommend deleting these data points. If the study was designed to detect efficacy at this timepoint, would it be appropriate to identify this additional timepoint on the y-axis?

DTOP Response: *The graphs for Study 1 have been revised by the applicant.*

Comment [CGC20]: OPDP Comment: We recommend communicating the dose and duration used in each of these treatment groups. We also recommend communicating the demographics of patients evaluated in this study, if possible.

DTOP Response: *Omidria is administered via dilution into irrigating solution used during cataract surgery or intraocular lens replacement surgery. Dosing and average duration information is potentially misleading.*

Comment [CGC21]: OPDP Comment: Figures (b) (4) refer to "OMS302." For clarity, we recommend defining this as Omidria.

DTOP Response: *Figures* (b) (4) *by the applicant.*

DMEPA
The Division of Medication Error Prevention and Analysis (DMEPA) provided a labeling review of the original package insert and original carton and container labeling

12. Labeling

Office of Compliance evaluations of the phenylephrine drug substance manufacturing facility and of the drug product facility are pending as of the date of this review. Once they are completed and found to be satisfactory:

NDA 205388, Omidria (phenylephrine and ketorolac injection) 1%/0.3% is recommended to be approved for:

- Maintenance of pupil size by preventing intraoperative miosis
- Reduction of postoperative pain

with the labeling (submitted 5/21/14) found in the Appendix at the end of this CDTL review.

13. Recommendations/Risk Benefit Assessment

RECOMMENDED REGULATORY ACTION:
Office of Compliance evaluations of the phenylephrine drug substance manufacturing facility and of the drug product facility are pending as of the date of this review. Once they are completed and found to be satisfactory:

NDA 205388, Omidria (phenylephrine and ketorolac injection) 1%/0.3% is recommended to be approved for:

- Maintenance of pupil size by preventing intraoperative miosis
- Reduction of postoperative pain

with the labeling (submitted 5/21/14) found in the Appendix at the end of this CDTL review .

RISK BENEFIT ASSESSMENT:
During surgical procedures, the admixed irrigation solution is administered either through a phacoemulsification surgical solution tubing set or via plastic syringe and needle. The intracameral space and to a lesser extent the surface of the eye are exposed to the irrigation admixture. This form of administration is expected to limit systemic absorption to only a small portion of the total drug substances present in a single dose of Omidria.

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 (ILR) surgery. The benefits outweigh the risks when Omidria is used during cataract surgery or intraocular lens replacement surgery for: 1) the maintenance of pupil size by preventing intraoperative miosis, and 2) the reduction of postoperative pain.

RECOMMENDATION FOR POSTMARKETING RISK MANAGEMENT ACTIVITIES:
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.

Appendix – Labeling

Carton and Container

Vial Label

(b) (4)

11 Pages Have Been Withheld In Full As b4 (CCI/TS) Immediately Following This Page

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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
05/23/2014

WILEY A CHAMBERS
05/27/2014