CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA REVIEW AND EVALUATION

Application number:	205388
Supporting document/s:	1
Applicant's letter date:	July 30, 2013
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Product:	Omidria™ (Phenylephrine hydrochloride/ketorolac tromethamine)
Indication:	(b) (4) prevention of intraoperative miosis, and reduction of (b) (4) postoperative ocular pain during lens replacement surgery
Applicant:	Omeros
Review Division:	Transplant and Ophthalmology Product
Reviewer:	María I Rivera, PhD Ilona Bebenek, PhD (Pharmacodynamics/ pharmacokinetics studies)
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1 Executive Summary

1.1 Introduction

OMS302 is a fixed-dose combination product containing phenylephrine hydrochloride, an α1-adrenergic receptor agonist, and the nonsteroidal anti-inflammatory drug (NSAID) ketorolac tromethamine, a nonselective cyclooxygenase (COX) COX-1/COX-2 inhibitor. OMS302 is intended to be used as an additive to the irrigation fluid used in lens replacement surgical procedures of the eye to (b) (4) prevent surgical miosis, and reduce postoperative (b) (4) ocular pain (b) (4).

The drug substances in OMS302 have been used individually for many years. Phenylephrine hydrochloride was initially introduced into clinical use at least 75 years ago and ketorolac tromethamine (Toradol®) was first approved in 1989. There is extensive nonclinical and clinical experience using each of these agents, though OMS302 is the first drug product containing both agents for ocular use.

1.2 Brief Discussion of Nonclinical Findings

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, respectivley. 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.

1.3 Recommendations

1.3.1 Approvability

Approval is recommended.

1.3.2 Additional Non Clinical Recommendations

None

1.3.3 Labeling

Italic font indicates reviewer's edits.

8.1 Pregnancy

Pregnancy Category C - Animal reproduction studies have not been conducted with Omidria *or phenylephrine*. It is also not known whether Omidria can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Omidria should be used in pregnant women only if clearly needed.

Ketorolac, administered during organogenesis, was not teratogenic in rabbits or rats at oral dose [redacted] *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 recommended human ophthalmic dose (RHOD), respectively.* When administered to rats after Day 17 of gestation at oral doses up to [redacted] *.5 mg/kg/day (up to 740-times the plasma exposure at the RHOD), ketorolac produced dystocia and increased pup mortality.*

[redacted]

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

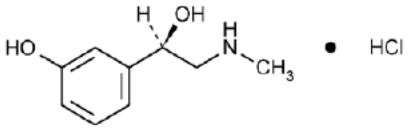
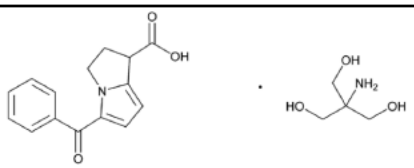
[redacted]

(b) (4)

2 Drug Information

2.1 Drug

Code Name: OMS302 (Fixed-dose combination product containing 12.37 mg/mL phenylephrine hydrochloride and 4.24 mg/mL ketorolac tromethamine)

Generic Name	Phenylephrine hydrochloride	Ketorolac tromethamine
CAS Registry Number	61-76-7	74103-07-4
Chemical Name	Benzenemethanol, 3-hydroxy-α-[(methylamino)methyl]-, hydrochloride (R)-; or (-)-*m*-Hydroxy-α-[(methylamino) methyl]benzyl alcohol hydrochloride	1*H*-Pyrrolizine-1-carboxylic acid, 5-benzoyl-2,3-dihydro, (±)-, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1); or (±)-5-Benzoyl-2,3-dihydro-1*H*-pyrrolizine-1-carboxylic acid, compound with 2-amino-2-(hydroxy-methyl)-1,3-propanediol (1:1)
Molecular Formula/Molecular Weight	$C_9H_{14}ClNO_2$/203.7	$C_{15}H_{13}NO_3 \bullet C_4H_{11}NO_3$/376.4
Structure		
Pharmacologic Class	A1 adrenergic receptor agonist	Non-selective cyclooxygenase 1 (COX-1)/cyclooxygenase 2 (COX-2) inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

IND 78,227 OMS302
DMF (b) (4); DMF (b) (4); DMF (b) (4); DMF (b) (4); DMF (b) (4)

2.3 Drug Formulation

OMS302 is a sterile, single-use drug formulation intended for admixture with sterile ophthalmic irrigating solutions. As shown in Table 1, 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 buffer (pH 6.3 ± 0.3). Each vial is filled to allow withdrawal of 4.0 mL of formulation concentrate for admixture with 500 mL of irrigation solution for a final concentration of 480 µM phenylephrine hydrochloride and 89 µM ketorolac tromethamine.

Table 1: Composition of OMS302 Dosage Form and Admixed Solution

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	0.0982
Ketorolac Tromethamine, USP	Drug Substance	17.0	4.24	0.0337
Citric Acid monohydrate, USP, Ph. Eur.	(b) (4)			
Sodium Citrate dihydrate, USP, Ph. Eur.				
Water for Injection, USP, Ph. Eur. [a]				
Sodium Hydroxide, NF, Ph. Eur. [b]				
Hydrochloric Acid, NF, Ph. Eur. [b]				
(b) (4)				

(b) (4)

USP = United States Pharmacopeia Ph. Eur. = European Pharmacopoeia NF = National Formulary

2.4 Comments on Novel Excipients

None

2.5 Comments on Impurities/Degradants of Concern

Several extractables and leachables from the glass vials and elastomeric stoppers were identified.

Glass Vial Extractables: For the extraction, approximately 5 grams of broken glass vials were added to 20 mL aliquots of OMS302, vehicle, or 2% nitric acid in water. Extraction samples were heated to 120°C for 30 minutes using a microwave extraction apparatus. The only measurable (b) (4), which was measured at (b) (4) of glass in the vehicle extraction solution. The applicant estimated a systemic human exposure of (b) (4) based on the human PK data in which the fraction of the total dose of OMS302 that appeared systemically was 1% or 0.04 mL (Module 2.7.2 Section 2 of the EDR document). Food and water often contain (b) (4) and estimated intake is (b) (4)

mg/day from food and (b) (4) mg/day from water[1], which is well above the estimated systemic exposure of (b) (4) for the OMS302 drug product.

Glass Vial Leachables: Samples of primary stability lot AA0661A, held under accelerated storage conditions of 40°C / 75% Relative Humidity (RH) for 6 months and long-term storage conditions of 25°C/60% RH for 6 months. (b) (4) was observed at (b) (4) of drug product in samples held at 40°C/75% RH vs (b) (4) in drug product samples held at 25°C/60% RH. (b) (4) was observed at (b) (4) in the drug product held at 40°C/75% RH versus levels below the LOQ of (b) (4) in drug product held at 25°C/60% RH. The applicant estimated a human exposure of (b) (4) based on the estimated maximum systemic dose of 1% OMS302. The median and mean daily intake of (b) (4) in the United States is (b) (4) respectively, for men and (b) (4), respectively, for women compared to the estimated maximum systemic exposure of (b) (4) with OMS302 use.

Elastomeric Stopper Extractables: Two extracts preparations were evaluated:

- Whole stoppers consisting of approximately 10 grams were refluxed in 100 mL each of bulk OMS302 and bulk vehicle for 4 hours.
- Whole stoppers consisting of approximately 1 gram were sealed into headspace vials and heated to 100°C for 30 minutes.

The extractable compounds and amount are shown in the table below. The applicant assumed that the maximum amount of each volatile present in each stopper will be incorporated into the drug product formulation. Estimated systemic human exposure is calculated by multiplying the maximum volatile present in each stopper by the estimated systemic dose (1%) for OMS302.

[1] Expert Group on Vitamins and Minerals (EVM). Safe Upper Levels for Vitamins and Minerals. UK: Committee on Toxicity; 2003 May]; http://cot.food.gov.uk/cotreports/cotjointreps/evmreport/

[2] (b) (4)

Table 2: Maximum Amount and Estimated Systemic Human Exposure of Stopper Extractables

Extractable Compound	Maximum Volatile per Stopper	Estimated Human Exposure
(b) (4)		

Elastomeric Stopper Leachables: Leachables evaluation of the following samples was conducted:

- primary stability lot AA0661A, held under accelerated storage conditions of 40°C / 75% RH in an inverted orientation for 6 months
- primary stability lot AA0661A, held under long term storage conditions of 25°C/60% RH in an inverted orientation for 6 months
- clinical lot 3-FIN-1180, held under accelerated storage conditions of 40°C / 75% RH in an inverted orientation for 15 months

(b) (4) was observed at (b) (4) of headspace (GC/MS) and (b) (4) was observed at (b) (4) in clinical lot 3-FIN-1180, held under accelerated storage conditions for 15 months. The applicant estimated a human exposure of (b) (4), based on the estimated systemic dose (1%) for OMS302. The applicant used the Product Quality Research Institute (PQRI) proposed Safety Concern Threshold (SCT) of 0.15 µg/day for lifetime daily exposure to organic leachables to support the safe levels of (b) (4) The applicant indicated the US Department of Human Health and Human Services has reported the estimated daily intake of (b) (4) to range from (b) (4).

Based on this analysis, where the estimated maximal levels were found to be below the estimated daily intake/exposure, the applicant does not plan to conduct further monitoring of the drug product for leachables/extractables. Although the applicant's analysis is considered acceptable for systemic toxicity risk assessment, a risk assessment for potential ocular (local) adverse effects needs to be considered separately.

[3]US Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological Profile for (b) (4) US Department of Health and Human Services; 2008 Sept; http://www.atsdr.cdc.gov/toxprofiles/index.asp

This reviewer calculated the ocular exposure for each leachable/extractable considering exposure to the eye of 4 mL OMS302 (Table 3). Given the irrigation procedure, most of OMS302 applied to the eye is continuously being removed. At the end of the surgical procedure, the anterior chamber is filled with OMS302 irrigation solution (4 mL OMS302 diluted in 500 mL irrigation solution). According to the public literature, the average volume of the anterior chamber is 200 µL[4]. As the irrigation solution will stay in the anterior chamber until the aqueous is replaced (turnover of aqueous = 1.2-2 hrs[5]), this is considered the period when potential toxicities may emerge. As shown in Table 3, the expected amounts in the anterior chamber are very small (nanogram to picogram amounts). The highest amounts were observed for (b) (4) ((b) (4) in the accelerated conditions; (b) (4) after long-term storage at ambient conditions). (b) (4)) has been investigated for intravitreal drug delivery and demonstrated good biocompatibility[6]. Therefore, the exposure to these extractables/leachables at these levels is not expected to be of main toxicological concern for the proposed dosing regimen.

Table 3: Estimated Systemic and Ocular Exposure of Leachables/Extractables

Source	Measured amount	Systemic exposure (1% OMS302)[a]	Maximal ocular exposure (4 mL OMS302)[b]	Ocular exposure in 200 uL aqueous volume[c]
(b) (4)				

[a] Calculated as "measured amount" x 4 mL OMS302 x 0.01; where 0.01 represents the 1% fraction of the total dose of OMS302 that appeared systemically
[b] Calculated as "measured amount" x 4 mL OMS302
[c] Calculated as "ocular exposure"/500 mL x anterior chamber value of 200 µL

[4] Fontana ST *et al*. *Arch Ophthalmol*, 98(10):1803-1808 (1980)
[5] https://www.nyee.edu/pdf/solomonaqhumor.pdf
[6] (b) (4))

[d]Not clear how the applicant calculated this value
[e]The applicant calculated a systemic exposure (b) (4)

2.6 Proposed Clinical Population and Dosing Regimen

Omidria is added to irrigation solution used during intraocular lens replacement surgery and is indicated for the (b) (4), prevention of intraoperative miosis, and reduction of (b) (4) postoperative ocular pain. Omidria must be diluted prior to use. For administration to patients undergoing intraocular lens replacement, 4.0 mL of Omidria (12.4 mg/mL of phenylephrine hydrochloride and 4.24 mg/mL ketorolac tromethamine) is diluted in 500 mL of standard irrigation solution (e.g., balanced salt solution).

2.7 Regulatory Background

End of phase 2 meeting was held on July 15, 2011. The Division agreed that the pharmacology and toxicology studies conducted by Omeros were sufficient to support the phase 3 program and subsequent NDA review.

3 Studies Submitted

3.1 Studies Reviewed

- Concentration-Ranging and Pharmacokinetic Study of Phenylephrine and Ketorolac Following Intraoperative Irrigation in a Primate Cataract Phacoemulsification Surgical Model: Mydriasis, Intraocular Inflammation, and Systemic Exposure (Study # RX06.02)
- Efficacy and Pharmacokinetic of OMS302 Following Intraoperative Irrigation in a Primate Cataract Phacoemulsification Surgical Model: Mydriasis, Intraocular Inflammation, Intraocular Pressure, and Systemic Exposure (Study # RX07.03)
- A Time Course and Dose-Dependent Response Study of Mydriasis following Intracameral Administration of OMS302 Drug Product (Study # RX07.06)
- Safety and Pharmacokinetic Evaluations of OMS302 Instilled as a Perioperative Ophthalmological Solution during Primate Phacoemulsification Surgery (Study # RX07.07)

3.2 Studies Not Reviewed

Analytical methods and validation reports

3.3 Previous Reviews Referenced

None

4 Pharmacology

Phenylephrine is an α1-adrenergic receptor agonist and, in the eye, acts as a potent vasoconstrictor and mydriatic agent by constricting ophthalmic blood vessels and the radial muscle of the iris. Ketorolac is an NSAID that inhibits both cyclooxygenase enzymes (COX-1 and COX-2), resulting in a decrease in tissue concentrations of prostaglandins to reduce pain and inflammation 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.

The safety profile of phenylephrine and ketorolac are well known based on the extensive clinical experience. The sponsor provided a review of the literature for both phenylephrine and ketorolac. Some excerpts are presented below.

Phenylephrine causes constriction of most vascular beds, which is the basis for its decongestant action. It reduces renal, splanchnic, cutaneous and limb blood flow, and increases coronary blood flow. Other well-known pharmacological effects include increased systolic and diastolic blood pressure after intravenous, subcutaneous or oral administration, and decreased intestinal motility.

Phenylephrine ophthalmic solutions (Phenylephrine Hydrochloride Ophthalmic Solution, 2.5% or 10% USP) are approved in the US as mydriatic agents for use in ophthalmic procedures, including ocular surgery, to provide refraction with minimal cycloplegia. Phenylephrine is also approved in a lower concentration (1%) in combination with the anti-muscarinic drug cyclopentolate for the induction of mydriasis (Cyclomydril®).

Changes in blood pressure and heart rate have been noted following the administration of eye drops containing 2.5% or 10% phenylephrine hydrochloride. In general, greater effects on both parameters were observed with 10% phenylephrine hydrochloride. Adverse reactions noted on the package inserts of ophthalmologic medications containing phenylephrine include hypertension, which can be severe in preterm infants, adults with orthostatic hypotension, and the elderly. In the elderly, cardiovascular adverse events including syncope, myocardial infarction, tachycardia, ventricular arrhythmia, and fatal subarachnoid hemorrhage have been reported. Ocular adverse reactions after topical administration include eye pain and stinging on instillation, temporary blurred vision, photophobia, rebound miosis, pigmented floaters, and conjunctival sensitization. Acute angle-closure glaucoma does occur rarely following the administration of phenylephrine for mydriasis but this is due to the mydriatic effect of phenylephrine.

The systemic effects of ketorolac are those common to the NSAIDS drug class. These include inhibition of platelet aggregation and prolongation of bleeding time, the potential to cause gastric damage and ulcers, serious cardiovascular thrombotic events, myocardial infarction, and stroke, and renal damage.

Ketorolac topical ophthalmic solutions are approved for the reduction of ocular pain and burning/stinging following corneal refractive surgery (Acular LS® [0.4%

ketorolac tromethamine]) and for the temporary relief of ocular itching due to seasonal allergic conjunctivitis (Acular® [0.5% ketorolac tromethamine]), and are also indicated for the treatment of postoperative inflammation in patients who have undergone cataract extraction (Acular® and Acuvail® [0.45% ketorolac]). In addition to hypersensitivity or cross-hypersensitivity reactions, serious adverse reactions to topical ocular NSAIDs include ocular bleeding and hyphemas. More commonly observed reactions include inflammation and/or edema of the cornea, iris, or conjunctiva. Keratitis has occurred and can be sight threatening. When used prior to or following cataract surgery, ketorolac does not induce significant increases in intraocular pressure (IOP). However, in some studies, increased IOP was reported as an adverse event with higher frequency in ketorolac versus vehicle groups, and instances of increased IOP have been recorded in the AERS database. On this regard, the label for Acuvail® reports increased IOP as one of the most common adverse reactions, although it indicates that some reactions may be the consequence of the cataract surgical procedure.

In addition to the extensive background literature that exists on the pharmacology of phenylephrine and ketorolac, Omeros conducted a series of studies evaluating the single agents and their combination in an *in vivo* surgical model relevant to the proposed clinical use. Three nonclinical primary pharmacology studies (Section 4.1) were conducted to support the distinct pharmacology of phenylephrine and ketorolac and their complementary modes of action during intraocular lens replacement with phacoemulsification in the African green monkey.

4.1 Primary Pharmacology

Concentration-Ranging and Pharmacokinetic Study of Phenylephrine and Ketorolac following Intraoperative Irrigation in a Primate Cataract Phacoemulsification Surgical Model: Mydriasis, Intraocular Inflammation and Systemic Exposure of Report (Study # RX06.02) The study consisted of two phases conducted in African green monkeys (*Chlorocebus aethiops*); treatment was done during a 20 minute (non-continuous) irrigation period of a phacoemulsification surgical model where either phenylephrine or ketorolac were delivered through the phacoemulsification needle (in buffered saline solution [BSS]). Phase I evaluated the mydriatic and anti-inflammatory effect of phenylephrine and four monkeys per group (2 males and 2 females) were treated with either BSS or phenylephrine (3, 10, 30 or 90 µM in BSS); only two monkeys per group (one per sex) were assigned to the 3 or 90 µM treatments. Phase II evaluated the mydriatic and anti-inflammatory effects of ketorolac and four monkeys per group (2 males and 2 females) were treated with BSS or ketorolac (3, 10, 30 µM) with the addition of 30 µM of phenylephrine for minutes 2 through 20 (the total treatment duration was 20 minutes). Efficacy endpoints included mydriasis (video pupil assessment), pachymetry, slit lamp, and inflammatory measures including laser flare photometry; a clinical exam and pharmacokinetic analysis were also performed. Maximal pupil dilation was achieved within approximately five minutes for all treatment groups.

In the phase I study, phenylephrine caused a dose-dependent increase in pupil diameter. Animals in groups treated with 10 µM, 30 µM and 90 µM phenylephrine

exhibited significantly higher mydriasis (pupil diameter) as compared to animals treated with low phenylephrine (3 μM) or tropicamide at the 14- and 18-minute timepoints ($F= 6.62$, $p <0.0002$; $F= 9.26$, $p<0.0001$ respectively; Student Newman-Keuls test $\alpha= 0.05$, $df = 23$).

In the phase II study, there was a rapid 1-2 mm increase in pupil diameter within 30 seconds of the start of perfusion followed by a less rapid concentration-independent rise between 30 seconds and 2 minutes. Given that no statistical differences were seen between the ketorolac and BSS-treated animals, initial dilation is thought to be a result of viscoelastic clearance and the hydrodynamic effects of irrigation/aspiration. After introduction of 30 μM phenylephrine, maximal dilation was observed within 4 minutes. Significant differences in pupil dilation were seen between the ketorolac high-dose and BSS groups and the ketorolac low-dose and mid-dose groups at the 14- and 18-minute timepoints, however the difference was attributed to the limited sample size and reflective of inter-animal and inter-procedure differences. At both phases, the pupil constricted following lens replacement at the end of the procedure.

In the phase II study, there was a consistent trend for a reduction in the flare measurements in the mid-dose and high-dose ketorolac groups (statistically significant only at 4.5 hours for combined mid-dose and high-dose ketorolac groups) as compared to the BSS control group.

Plasma samples were collected at time 0, 20, 50, 80 and 140 minutes after initiation of irrigation. For phase I, only the 10 μM and 30 μM phenylephrine treatments resulted in detectable levels at the 20 minute timepoint (mean of 0.44 and 1.12 ng/mL, respectively); whereas no phenylephrine was detected at the high dose of 90 μM. These levels were below the lower limit of quantitation of 2 ng/mL. For phase II, measurable levels of ketorolac were observed at the 20 minute timepoint at the low (3 μM), mid (10 μM) and high (30 μM) concentrations (mean of 1.17, 1.68 and 4.61 ng/mL). At the 3 μM and 10 μM concentrations, ketorolac levels declined from 50 to 140 min after initiation of irrigation. Ketorolac levels at the high dose (30 μM) peaked in monkey plasma at the 80 minute timepoint with mean concentrations reaching 10.45 ng/mL, with levels decreasing to 2.21 ng/mL at the 140 min timepoint.

Efficacy and Pharmacokinetic Study of OMS302 Following Intraoperative Irrigation in a Primate Cataract Phacoemulsification Surgical Model: Mydriasis, Intraocular Inflammation, Intraocular Pressure, and Systemic Exposure (Study # RX07.03) Three to four monkeys *(Chlorocebus aethiops)*/sex/group were treated with either tropicamide (1 drop of 0.5%), BSS and placebo (20 mM sodium citrate buffer, pH 6.5, vehicle used for dilutions) or BSS and OMS302 (90 μM phenylephrine and 30 μM ketorolac) during the perfusion period of a phacoemulsification procedure (total perfusion duration 13 minutes). Efficacy endpoints included mydriasis, intraocular pressure and inflammatory measures including laser flare photometry up to one week after the initiation of the irrigation); a clinical exam and pharmacokinetic analysis (up to 140 minutes after the initiation of irrigation) were also performed.

Monkeys treated with OMS302 exhibited statistically significant ($p < 0.05$; Student Newman-Keuls test) increase in dilation (as compared to the tropicamide/placebo group) from the baseline until the last measured timepoint (13 minute timepoint) at almost all timepoints measured. The OMS302 treatment group had lower values of flare measures over time relative to the tropicamide control group, but did not achieve statistical significance ($p< 0.0097$; Student Newman-Keuls test) until the exclusion of animal X932 (which exhibited a more limited pupil dilation during anterior chamber irrigation, complicating lens removal) during the 2, 4.5, 24 and 48-hour timepoints. There was a trend toward lower pachymetry values (indicating less corneal swelling) at all timepoints in the OMS302-treated groups compared to the tropicamide controls when the data were normalized to change from baseline, but statistical significance was only observed at the 4.5 hour timepoint ($p<0.05$; student's T test). While levels of phenylephrine were undetectable 20, 50, 80 and 140 minutes after initiation of irrigation (lower limit of quantitation = 2 ng/mL), levels of ketorolac were measurable from the 20 minute timepoint up to the last timepoint of 140 minutes (2.89 and 0.40 ng/mL, respectively).

A Time Course and Dose Response Study of Mydriasis following Intracameral Administration of OMS302 Drug Product (Study # RX07.06) – Three groups of four monkeys (*Chlorocebus aethiops*; 2/sex) were treated with OMS302 at three different concentrations of phenylephrine:ketorolac combination (90:30 µM; 268:89 µM; 1165:89 µM) via intracameral injection. According to video pupil data (measured for 10 minutes), OMS302 delivery into the anterior chamber resulted in a rapid onset of mydriasis (first 60 seconds), which was maintained throughout the ten minute period during which the video occurred. The observed differences between the low- and high-dose groups and the overall observed impact of all doses on mydriasis confirmed a dose-dependent effect of the OMS302 combination product containing phenylephrine and ketorolac on the amplitude of post-administration mydriasis. Pupil diameter returned to baseline within 24 hours in all animals.

Pharmacokinetic results indicated that systemic phenylephrine and ketorolac levels were below the lower limit of quantitation of 2 ng/mL at baseline, 10 and 30-minute timepoints for all animals that received the mid-dose and all but 2 animals that received the low dose. The exceptions were low dose animal X819 at the 30 minute timepoint and low dose animal Y173 at the baseline The sponsor stated the anomalous levels of phenylephrine and ketorolac at baseline may reflect a sample contamination, mislabeling or analytic error. The sponsor stated these possibilities may also explain the 30 minute data for animal X819. For animals treated with the highest dose of OMS302, the highest levels in plasma were detected at baseline, not consistent with expectations. Retests indicated a possible contamination of unknown origin in the current samples. Therefore, the pharmacokinetic data from this study is not considered reliable.

4.2 Secondary Pharmacology

See summary presented under Section 4.

4.3 Safety Pharmacology

See summary presented under Section 4.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

The systemic exposure after ocular administration of OMS302 is presented under Sections 4.1 and 6.1 of this review. The following are excerpts of published literature findings or label information from previously approved products provided by the applicant, considered of relevance to the current application.

Phenylephrine:

- The PK of a single oral dose of 10 mg phenylephrine hydrochloride was evaluated in twelve healthy volunteers and the results showed a T_{max} of less than one hour and mean maximum plasma concentration of 1.8 ng/mL[7].

- In human subjects undergoing vitreoretinal surgery, phenylephrine was detectable in plasma samples, with peak levels ten minutes after topical ocular administration. Drug levels after 10% drops (range: 1 to 24 ng/mL) were generally higher than after 2.5% drops (range: 1 to 6 ng/mL). In all subjects, phenylephrine levels declined by > 80% after one hour[8].

- A study in human subjects with healthy eyes reported plasma levels ranging from 0 to 3.3 ng/mL 20 minutes after instillation of 10% phenylephrine hydrochloride drops[9]. There was a trend toward lower levels with a smaller drop size (10 µL vs. 30 µL).

Ketorolac:

The ocular pharmacokinetics of ketorolac is summarized in the "Pharmacokinetics" section of the both the Acular® and Acuvail® labels as follows [Acular® PI 2012; Acuvail® PI 2012]:

- Two drops of 0.5% ketorolac tromethamine ophthalmic solution instilled into the eyes of patients 12 hours and 1 hour prior to cataract extraction achieved a mean ketorolac concentration of 95 ng/mL in the aqueous humor of 8 of 9 eyes tested (range 40 to 170 ng/mL).

- One drop of 0.5% ketorolac tromethamine ophthalmic solution was instilled into 1 eye and 1 drop of vehicle into the other eye TID in 26 healthy subjects. Five (5) of

[7] Ptácek P *et al*., *J Chromatogr B Analyt Technol Biomed Life Sci*, 858(1-2):263-268(2007). Epub 2007 Sep 14.
[8] Kumar V *et al*., *Arch Ophthalmol*, 104(8): 1189-1191 (1986)
[9] Whitson JT *et al*., *Am J Ophthalmol*, 115(3): 357-359 (1993)

26 subjects had detectable concentrations of ketorolac in their plasma (range 11 to 23 ng/mL) at Day 10 during topical ocular treatment.

- The range of concentrations following TID dosing of 0.5% ketorolac tromethamine ophthalmic solution are approximately 4 to 8% of the steady state mean minimum plasma concentration observed following four times daily oral administration of 10 mg KE in humans (290 ± 70 ng/mL).

The average ketorolac C_{max} reported in the FDA approved label for Toradol® is 870 ng/mL after a single 10 mg oral dose, 1140-4550 ng/mL after a single 15-60 mg intramuscular dose, and 2470-4650 ng/mL after a single 15-30 mg intravenous bolus.

According to the applicant, plasma concentrations of phenylephrine were undetectable at all timepoints for all but one subject who received OMS302 in clinical study # OMS302-ILR-004 conducted under this NDA. The only subject with detectable phenylephrine had a value of 1.7 ng/mL at the pretreatment timepoint, presumably due to exposure to the preoperative phenylephrine hydrochloride 2.5% eye drops and not due to OMS302. Lower values of 1.2 to 1.3 ng/mL were observed in this subject over the subsequent 2 hours. These concentrations (observed in only one subject) are comparable or below those reported after oral administration of a 10 mg dose or topical ocular administration of 2.5% or 10% phenylephrine hydrochloride drops (overall plasma level range of 0.65-24 ng/mL).

In clinical study # OMS302-ILR-004, ketorolac was detected in 10 of 14 subjects treated with OMS302 and 1 of 12 subjects treated with placebo. The sponsor claims that the ketorolac measured in some subjects at the 24-hour postsurgery timepoint may have been due to application of postoperative ketorolac ophthalmic eye drops scheduled to begin the day after surgery, e.g., the placebo-treated subject. The amount of ketorolac detected was low, in the 1 to 4 ng/mL range. These levels are lower than what is reported with 0.5% ketorolac eye drops (11 to 23 ng/mL), and approximately 70-fold below trough levels reported following oral administration (290 ± 70 ng/mL; Toradol® label).

6 General Toxicology

6.1 Single-Dose Toxicity

Study title: Safety and Pharmacokinetic Evaluations of OMS302 Instilled as a Perioperative Ophthalmological Solution during Primate Phacoemulsification Surgery

Study no.: RX07.07
Study report location: EDR Module 4.2.3.1
Conducting laboratory and location: (b) (4)

[redacted] (b) (4)

Date of study initiation: August 24, 2007
GLP compliance: Yes
QA statement: Yes
Drug, lot #, and % purity: OMS302 (45 mM [9.16 mg/mL] phenylephrine hydrochloride and 15 mM [5.65 mg/mL] ketorolac tromethamine), lot # NFF-0050, 101.9% pure for phenylephrine and 102.1% pure for ketorolac

Phenylephrine CF drug product (phenylephrine hydrochloride 450 mM [91.6 mg/mL]), lot # NFF-0048, 99.4% pure

Key Study Findings

- Intracameral delivery of OMS302 during lens replacement surgical procedures in nonhuman primates was not associated with any test article related toxicities.
- The local effects observed were considered related to the irrigation procedure or surgical trauma.
- Low systemic exposure to phenylephrine and ketorolac was observed.
- The NOAEL was the highest dose evaluated, i.e., 7200 µM (1466.6 mg/mL) phenylephrine and 900 µM (338.8 mg/mL) ketorolac.

Methods

Doses: 0 (balanced salt solution [BSS])
720 µM (146.7 µg/mL) phenylephrine and 90 µM (33.9 µg/mL) ketorolac
2160 µM (440 µg/mL) phenylephrine and 270 µM (101.6 µg/mL) ketorolac
7200 µM (1466.6 µg/mL) phenylephrine and 900 µM (338.8 µg/mL) ketorolac

Note: These are final concentrations in 500 mL irrigating BSS solution.

Frequency of dosing: Once over an ~30-minute irrigation period
Route of administration: Anterior chamber of the right eye by intracameral instillate with a syringe and by continuous irrigation *via* the phacoemulsification handpiece
Dose volume: The test solutions were administered initially by a 150-µl (from the irrigation bottle) direct injection into the anterior chamber followed by irrigation of the anterior chamber through the phacoemulsification probe.

	The test solutions in the 500-mL irrigation bottles were administered into the anterior chamber of the eye over a 30-minute period by continuous irrigation using the phacoemulsification instrument. Total irrigation volumes were on average ~200 mL for the duration of the surgery.
Formulation/Vehicle:	20 mM sodium citrate buffer (pH 6.5±0.5)
Species/Strain:	African green monkey *(Chlorocebus sebaeus)*
Number/Sex/Group:	3
Age:	At least 4 years old
Weight:	4.15 – 5.81 kg for males; 3.18 - 4.36 kg for females
Satellite groups:	None
Unique study design:	All animals underwent a surgical procedure on Day 0 to replace the intraocular lens. The animals were maintained on study for a 14-day recovery period. To allow sufficient pupil dilation to perform phacoemulsification surgery in BSS control group, animals were pre-treated with two drops of 1% tropicamide 20 minutes prior to the initiation of anterior chamber irrigation with BSS alone. An 8:1 fixed-concentration ratio of the active pharmaceutical ingredients in the OMS302 (45:15 mM) test article was evaluated. To achieve the 8:1 fixed-concentration ratio, Phenylephrine CF drug product (phenylephrine HCl: 450 mM) was also prepared and used to increase the concentration of phenylephrine in the irrigation solutions. The OMS302 and Phenylephrine CF were diluted with balanced salt solution (BSS) to provide for approximate final concentrations in the 500-mL irrigation bottles. The study report states that the African green monkey was selected for this study because the size of the instruments and lenses needed to perform lens removal and replacement surgery preclude the use of smaller primate species.
Deviation from study protocol:	None with an impact on data interpretation

Observations and Results

Mortality (2x/day) - None

Clinical Signs (Daily) – It was stated in the study report that there were no test article-related effects.

There were no test article-related findings in heart rate, respiratory rate, changes in pO_2, or rectal temperature measured during the surgery (intraoperative).

Body Weights (Prior to surgery and pre-sacrifice on Day 14) – No test article-related effects were observed in mean body weights.

Feed Consumption (Conducted with the daily clinical observations) – It was stated in the study report that feeding was transiently reduced for 36 hours in 3 animals following the surgical procedure (doses not identified), after which feeding returned to baseline.

Ophthalmoscopy (Slit Lamp at ~2, 4.5, and 24 hours and Day 14 in the operative [right] eye following the surgical procedure) - Flare assessments were consistent with laser flare photometry measures (see below). The mid-dose showed higher anterior chamber flare compared to BSS control or low and high-dose groups at the 2-24 hour evaluations (Table 4). The flare was reduced by Day 14.

Table 4: Mean Slit Lamp Flare Results

	baseline	2 hrs	4.5 hrs	24 hrs	336 hrs
control	0.00	1.00 ± 0.26	1.00 ± 0.26	1.00 ± 0.26	0.83 ± 0.17
720:90 µM	0.00	0.50 ± 0.22	0.50 ± 0.22	0.83 ± 0.17	0.17 ± 0.17
2160:270 µM	0.00	1.67 ± 0.21	1.33 ± 1.33	1.67 ± 0.21	0.33 ± 0.21
7200:900 µM	0.00	0.83 ± 0.31	0.67 ± 0.21	1.33 ± 0.21	0.50 ± 0.22

Table 15: Mean slit lamp flare assessments ± standard error for the right (operative) eye in the tropicamide control and OMS302 treatment groups.

Likewise, mean scale values of anterior cell assessments revealed time-related differences – reflecting the effect of surgical intervention – but no difference between groups. Increased number of cells was observed during the 2-24 hour evaluation period in all groups including BSS controls. Recovery was observed by Day 14.

The pupil diameter was higher (36-87%) than that observed in BSS controls (pretreated preoperatively with tropicamide) in all OMS302-treated groups at the 2 and 4.5 hour evaluations. There was no statistically significant difference in the degree of mydriasis among all OMS302-treated groups. The values returned to baseline in tropicamide control as well as in OMS302-treated groups by 24 hours, indicating minimal residual treatment-associated mydriatic effect.

Additional Ocular Evaluations:

Video Pupil Assessment - The time course of the mydriatic effect was documented through video recording of the pupil during the perfusion procedure. Measurements were made at baseline and at 30 second to 2 minute intervals up to 33 minutes after the initiation of the perfusion procedure. In the case of the control group, pupil dilation was achieved with preoperative topical application of tropicamide eye drops. The control animals were pre-treated with two drops of 1% tropicamide 20 minutes prior to the initiation of anterior chamber irrigation with BSS alone.

Intracameral delivery of OMS302 resulted in a rapid pupil dilation within 30 seconds, with dilation increasing to 6.76 ± 0.15, 7.03 ± 0.25, and 7.29 ± 0.15 mm (± SD), at the low, mid, and high-dose, respectively, compared to a pupil diameter of 5.18 ± 0.18 mm in the control group (all changes were statistically significant compared to control). Subsequently, mean pupil diameter was greater in all OMS302 treatment groups than the control group at all timepoints following the initiation of the anterior chamber perfusion. However, statistical significance was only observed at the mid-dose at the 3:30, 4:00, 4:30 and 10:00 minute timepoints.

Flare Photometry - Laser flare photometry, a measure of anterior chamber inflammatory protein abundance, was performed at baseline, and ~2, 4.5, and 24 hours and 14 days after the initiation of the surgical procedure. Flare was increased in all groups including controls reflecting inflammation induced by the surgery (Table 5). The OMS302 mid-dose group had higher flare relative to the control (2.6 to 4-fold) at all post-surgical timepoints, achieving significance at 2, 4.5, and 24 hours. This effect resolved by Day 14. It was stated in the study report that the finding reflected greater surgery associated trauma compared to the other groups and therefore, it was not considered test article related. According to page 32 of the study report, each animal underwent the surgical procedure on a different day, which makes it difficult to expect that all animals will show the same surgical associated trauma. However, given the lack of a similar effect at the high dose, this reviewer agrees it is difficult to attribute the finding to the test article.

Table 5: Mean Flare Photometry Results

Treatment Group	Right (Operative) Eye					Left Eye	
	Baseline	2 hours	4.5 hours	24 hours	14 days	Baseline	14 days
Control	3.6 ± 1.0	35.3 ± 12.1	41.5 ± 10.5	48.4 ± 11.0	38.4 ± 5.9	7.3 ± 1.0	5.5 ± 0.9
720:90 µM	5.6 ± 0.9	34.1 ± 12.5	28.1 ± 8.3	53.3 ± 15.6	26.2 ± 8.0	5.1 ± 1.5	8.2 ± 2.2
2160:270 µM	4.3 ± 0.9	148.0 ± 38.5*	107.9 ± 25.4*	198.1 ± 49.7*	50.9 ± 18.5	5.5 ± 1.2	6.0 ± 1.8
7200:900 µM	3.2 ± 0.5	49.0 ± 23.4	29.4 ± 4.8	68.6 ± 16.8	41.1 ± 9.9	7.3 ± 1.7	5.5 ± 1.3

Mean flare measures (photon units/ms) ± standard error for the right (operative) eye and left eye in the tropicamide control and PE/KE treatment groups.

* indicates significant difference between the mid-dose (2160:270 µM) group versus all other treatment groups (Student Newman-Keuls test, $\alpha = 0.05$, df = 18).

Corneal Pachymetry (Baseline, and at ~2, 4.5, and 24 hours after the initiation of the surgical procedure and at Day 14 on the operative [right] eye; baseline and Day 14 on the non-operative control eye) - In all groups including controls, corneal thickness was increased in the operative eye at all evaluations timepoints, with peak effect occurring at 24 hrs. There was no significant difference between control and test article-treated groups (with the exception noted below), suggesting the increased in corneal thickness reflected surgery-associated corneal edema.

The only significant difference between groups was observed at the 4.5 hour timepoint when the mean pachymetry measure in the mid-dose group was reduced relative to the mean measures in all other treatment groups (Table 6). As noted above for flare photometry, given the lack of a similar effect at the high dose, this reviewer believes it is difficult to attribute the finding to the test article.

Table 6: Mean Pachymetry Results

Treatment group	right (operative) eye					left eye	
	baseline	2 hrs	4.5 hrs	24 hrs	336 hrs	baseline	336 hrs
Control	442.7±9.1	579.0±14.3	578.7±16.1	625.3±31.2	535.2±8.9	446.0±8.3	445.2±8.3
720:90 µM	450.5±9.5	556.7±17.0	568.0±14.4	606.5±35.4	529.3±19.6	452.3±9.6	449.8±8.7
2160:270 µM	438.3±5.1	502.2±47.0	522.3±14.8*	580.3±22.7	516.8±8.3	443.5±9.7	436.3±7.0
7200:900 µM	433.7±10.1	575.0±50.7	596.5±15.8	588.3±31.2	517.2±15.3	446.0±10.3	445.2±9.1

Table 13: Mean pachymetry measures (µm) ± standard error for the right (operative) eye and left eye in the tropicamide control and OMS302 treatment groups.
* indicates significant difference between the OMS302 2160:270 µM group versus all other treatment groups (Student Newman-Keuls test, $\alpha = 0.05$, df = 20).

Tonometry (Baseline, and at ~2, 4.5, and 24 hours after the initiation of the surgical procedure and at Day 14 on the operative [right] eye; baseline and Day 14 on the non-operative control eye) - Compared to baseline, all groups including controls showed reduced intraocular pressure at all timepoints. There were no toxicologically significant differences between control and test article-treated groups.

ECG (ECG, heart rate, respiratory rate, pO2 and rectal temperature recorded throughout the phacoemulsification procedure at pre-perfusion and at 0-10, 10-20, 20-30, and 30-40 min after initiation of the irrigation) – No test article-related effects

Hematology and coagulation (Pretest, 24-96 hours and 12-14 days after completion of the irrigation procedure) – No test article related effects were observed. Three control and 2 low-dose animals showed high APTT values (95.8-212 sec vs. 21.7-31.9 sec in normal controls) at pretest and/or on Day 11-14 post-irrigation, suggesting a problem with the assay and/or samples. The elevation in APTT was accompanied by elevated PT values (106 sec vs. 9.8-14.7 sec in normal controls) in one control and one low-dose animal.

Clinical Chemistry (Pretest, 24-96 hours and 12-14 days after completion of the irrigation procedure) – AST was elevated in most animals from all groups including tropicamide controls at the 24-96 hour timepoint. The elevation returned to baseline by 11-14 days. It was stated in the study report that the elevation resulted from the surgical intervention and repeated ketamine sedation rather than from treatment with the test article. Given the observation of the finding in control animals, this explanation is considered plausible. γ-GT was above baseline range in one low-dose and one mid-dose male at the 24-96 hour timepoint. However, the lack of a similar effect at the high-dose suggests the elevation was not test article-related.

Urinalysis (Prior to terminal sacrifice) – Overall, females at all OMS302-treated groups showed decreased urine volumes compared to control group values (4.5-5.0 mL, 2.5-5.0 mL, 2.5-5.0 mL, 1-5.5 mL in controls, low, mid, and high OMS302 dose, respectively). Given the lack of any effect in any other urine or clinical chemistry parameters, the decrease was considered unrelated to the test article.

Gross Pathology (All animals, Day 14) – It was stated in the study report that no test article-related gross abnormalities were observed.

Organ Weights (heart, kidneys, liver, lungs, spleen, brain, and eyes with optic nerve from all animals and all gross lesions) – No test article-related effects were observed in mean absolute and relative to body weight values.

Histopathology (Both eyes with attached optic nerves from all animals) –

Adequate Battery – Yes, given that the systemic exposure was within the range of the levels observed in humans after administration of ocular phenylephrine drops (0.86-24 ng/mL; Table 10) or oral, intramuscular, or intravenous ketorolac (870-4650 ng/mL; Toradol® label).

Peer Review - No

Histological Findings - No test article-related microscopic findings were observed in the eye tissues. All microscopic findings were consistent with those expected 14 days post-phacoemulsification surgery, and all findings were observed with similar incidence and severity in eyes of treated versus control animals. There were no microscopic findings in the left eye or in optic nerves of either eye.

Toxicokinetics (Pre-irrigation and 0.5, 2, 4.5, and 24 hours after the initiation of the irrigation) – Plasma phenylephrine and ketorolac levels were measurable across treatment groups. At the low and mid-dose, phenylephrine was detected in the plasma only at the 0.5 hr timepoint. At the high-dose, T_{max} also occurred at 0.5 hr with plasma levels declining following irrigation to levels below the lower limit of quantitation (<2 ng/mL) by 24 hours. An exception was a high-dose female (#X944) with phenylephrine levels of 123 ng/mL at the 24-hr timepoint. Given lower values at earlier timepoints (22.9 ng/mL at 0.5 hr down to 8.48 ng/mL at 4.5 hrs) in this female, this seems to reflect a problem with the assay. At C_{max}, phenylephrine levels ranged from 0 to 6.9 ng/mL at the low-dose group, 5.1 to 9.2 ng/mL at the mid-dose group and 15 to 38 ng/mL at the high-dose group.

The T_{max} for ketorolac also occurred at 0.5 hrs. For low- and mid-dose animals, measurable concentrations were still observed at 2 hrs or 4.5 hrs. In 3 out of 6 high-dose animals, ketorolac was still detected at 24 hrs. C_{max} levels ranged from 11.6-47.9 ng/mL, 29.5-55.1 ng/mL, and 72.3-189.3 ng/mL in the low-, mid-, and high-dose groups, respectively.

Dosing Solution Analysis – The percent label claim obtained for both phenylephrine HCl and ketorolac tromethamine in all the vials of OMS302 drug product ranged from 100.8% to 106.6% and Phenylephrine CF drug product reserve samples ranged from 99.9% to 102.8%.

The test article irrigation solutions were also analyzed for potency. The percentage of each API recovered from the irrigation samples were below acceptable levels for most samples (i.e., between 45.3% – 69.1% below the label claim for phenylephrine HCl and 45.0%-76.0% for ketorolac tromethamine).

The irrigation samples were initially frozen at -20 ºC as per protocol and then transferred into in liquid nitrogen (approx. -200 ºC) and shipped to Omeros on dry ice (approx. -78 ºC) for analysis. The samples were held at 2-8ºC at Omeros for three days prior to analysis. These storage conditions were identified as protocol deviations. A new set of samples was obtained from (b) (4). These retest samples were taken from the original irrigation solution bottles used in the toxicity study, which were stored at room temperature. Two mL of each of the samples were transferred with glass transfer pipettes into glass vials, shipped in glass vials on ice (2-8°C) and analyzed immediately upon arrival at Omeros.

Upon retesting, the irrigation solutions showed percent recovery concentrations of phenylephrine HCl that ranged from 93.0-108.0% and ketorolac tromethamine that ranged from 95.1-100.2% of the expected target concentration range.

7 Genetic Toxicology

No genotoxicity studies were performed by the sponsor with OMS302. The sponsor relied on findings from the published literature and/or labels for FDA approved products. The proposed label does not include any genotoxicity data (see comment under Section 8 Carcinogenicity).

Studies conducted by the National Toxicology Program[10] demonstrated that phenylephrine was not mutagenic in *Salmonella typhimurium* (with or without S9 activation). Mutagenicity assessments using the mouse lymphoma L5178Y/TK$^{+/-}$ assay were judged to be equivocal because the high doses of phenylephrine used were toxic to the cells and the results were not reproduced in a second study. A positive response was noted in the first trial without metabolic activation at the high dose of 1,500 µg/mL (relative total growth was 12.2%). Phenylephrine induced sister-chromatid exchange at ≥1500 µg/mL (-S9 fraction) but was negative for the formation of chromosomal aberrations in Chinese hamster ovary cells at doses up to 2,500 µg/mL (-S9 fraction) and 10,000 µg/mL (+S9 fraction).

[10] National Toxicology Program Technical Report No. 322, Toxicology and Carcinogenesis Studies of Phenylephrine Hydrochloride in F344/N Rats and B6C3F$_1$ Mice, NIH Publication No. 87-2578, January 1987, http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr322.pdf#search=phenylephrine%20hydrochloride

Information in the label for Tramadol®, Acular® and Acuvail® state that ketorolac tromethamine was not mutagenic in the Ames test, unscheduled DNA synthesis and repair, and in forward mutation assays. Ketorolac tromethamine did not cause chromosome breakage in the *in vivo* mouse micronucleus assay. Ketorolac tromethamine increased the incidence of chromosomal aberrations in Chinese hamster ovarian cells at ≥1590 µg/mL.

Four process impurities (Table 7), resulting from the synthesis utilized by each drug substance manufacturer, have been observed in drug substance batches from the validated manufacturing processes above the reporting threshold of 0.05% specified in ICH Q3A(R2) Guidance.

Table 7: Ketorolac and Phenylephrine Process Impurities

Impurity	Name	Structure
		(b) (4)

Cont. Table 7

Impurity	Name	Structure
		(b) (4)

(b) (4) has also been confirmed as a degradation product in the OMS302 drug product formulation. The identified process impurities noted by the drug substance manufacturers of ketorolac and phenylephrine are controlled at (b) (4) (Table 8). The specified impurity identified in OMS302 drug product, (b) (4), is controlled at (b) (4)

Table 8: Summary of Specified Impurities in the OMD302 Drug Product

Specified Related Substance	Specification(s) Used for Control	Specification Limits	ICH Q3A(R2) Qualification Threshold	ICH Q3B(R2) Qualification Threshold
(b) (4)			0.15%	Not Applicable
			0.15%	1.0%
			0.15%	Not Applicable
			0.15%	Not Applicable

NMT = not more than

Note: *The ICH Q3B(R2) qualification threshold for* (b) (4) *(based on a ketorolac tromethamine dose of 16.97 mg or 4.24 mg/mL x 4 mL) is* (b) (4)

A risk assessment regarding patient exposure to potential genotoxic impurities was carried out by the sponsor. The maximum systemic exposure for each impurity was then compared to the Threshold of Toxicological Concern (TCC) of 120 µg/person/day for genotoxic impurities for drug products with duration of exposure of less than one month *(Draft Consensus Guidance ICH M7, 2013).* The maximum systemic exposure of each specified related substance was derived from the specification limit for the impurity and a maximum systemic dose of 0.49 mg of phenylephrine hydrochloride and 0.17 mg ketorolac tromethamine (based on human PK data in which the fraction of the total dose of OMS302 that appears systemically was 1% or 0.04 mL; Module 2.7.2 Section 2 of the EDR document). The comparison is shown in Table 9.

Table 9: Comparison of OMS302-Related Substances with the Threshold of Toxicological Concern for Impurities with Genotoxic Potential

OMS302 Related Substances	Maximum Systemic Dose of Drug	Related Substance Specification Limit	Maximum Systemic Exposure of Related Substance	Threshold of Toxicological Concern (TTC) for Drug Products with a Duration of Exposure of Less than One Month
(b) (4)				

The sponsor concluded that this comparative summary demonstrated that the maximum potential systemic levels of all OMS302-related substances are not expected to exceed the TTC level and, consequently, do not pose an unacceptable risk to patients. Additionally, it is noted that the total of (b) (4) for the maximum systemic exposure of all related substances is also well below the TTC of 120 µg/person/day.

Assuming the 1% (0.04 mL) estimation for systemic OMS302 exposure in humans is correct, the above analysis is considered acceptable for systemic risk assessment. However, the systemic intake levels do not apply to ocular tissues exposed via ocular routes. There is a paucity of available data regarding the potential for ocular carcinogenicity following ocular administration, upon which to establish a safe threshold. However, there are several lines of evidence to support minimal genotoxic concern for these potential impurities:

- The product is indicated for single use and it is mostly removed from the eye because of the irrigation method of delivery.
- Through 18 months of long-term storage conditions of 5°C/ambient relative humidity and 25°C/60% RH of OMS302 phase 3 clinical lot 3-FIN-1180, no degradation products were observed above the (b) (4) reporting threshold utilized during clinical investigation.
- Through 6 months of storage of OMS302 phase 3 clinical lot 3-FIN-1180 under accelerated conditions (40°C/75% RH), only a single degradation product, (b) (4), was observed above the reporting threshold of (b) (4) (levels of (b) (4) at 3 months and (b) (4) at 6 months).

- The specification limit for [redacted] (b) (4) of [redacted] (b) (4) is the same as that on a previously approved ocular ketorolac tromethamine product.
- The specification for both [redacted] (b) (4) and [redacted] (b) (4) of [redacted] (b) (4) is similar to that found on a previously approved phenylephrine product.

The specification limit for [redacted] (b) (4) of [redacted] (b) (4) in the drug product is higher than that in previously approved ocular ketorolac tromethamine products. Given the findings in clinical lots under accelerated conditions of up to [redacted] (b) (4) the reviewer recommends lowering the specifications.

Note: *See CMC review for more detail information about specifications for phenylephrine and ketorolac drug substances and OMS302 drug product.*

8 Carcinogenicity

No carcinogenicity studies were performed by the sponsor with OMS302. The sponsor relied on findings from the published literature and/or labels for FDA approved products, as noted below. Consistent with the labels for NDA 203-510 (Phenylephrine Hydrochloride Ophthalmic Solution 2.5% and 10%; approved on March 2013) and NDA 203-826 (Phenylephrine Hydrochloride IV Injection; approved on December 2012), both indicated for short-term use, the sponsor has not included Section 13 Carcinogenicity in the proposed OMS302 label. Data for ketorolac was also not included in the proposed label. Given the single day use of the product, lack of a reason for concern from the available genetic toxicity and carcinogenicity data, and long history of clinical use, the inclusion of these data in the label is not considered clinically relevant.

Regarding phenylephrine, the sponsor made reference to carcinogenicity studies conducted by the National Toxicology Program (Ref. 10 above). Briefly, the carcinogenicity of phenylephrine was studied in two-year studies in mice and rats. The doses used were 0, 620, and 1,250 ppm phenylephrine in the diet in rats and 0, 1,250, and 2,500 ppm in mice. There was no evidence of carcinogenicity in mice or rats. Based on the feed consumed, the maximum doses correspond to 50 mg/kg/day (rats) and 270 mg/kg/day (mice). The following non-neoplastic lesions were considered related to phenylephrine hydrochloride: chronic focal inflammation of the liver and perivascular cuffing of the lung at both doses in male and female rats, inflammation of the prostate at both doses in male rats, and focal cellular change in the liver in high-dose male mice.

Regarding ketorolac, the sponsor summarized the information in the labels for Acular®, Acuvail®, and Toradol®.

- An 18-month study in mice at oral doses of ketorolac equal to the parenteral maximum recommended human dose (MRHD; 2.4 mg/kg/day) and a 24-month study in rats at oral doses 2.5-times the parenteral MRHD showed no evidence of tumorigenicity (Acular® PI 2004).

Note: According to the Acular® PI, the doses used in mice and rats were 2 mg/kg/day and up to 5 mg/kg/day, respectively. The sponsor conversion factors are incorrect. Based on body surface area, the safety margins are 14.8-fold in mice and 2.96-fold in rats.

- In a 78-week study in mice, at doses up to 1- and 3-fold of maximum intramuscular and oral doses, ketorolac did not increase the risk of developing tumors (Toradol PI 2007).

  Note: According to the Toradol® PI, the maximum oral daily dose is 40 mg/day (0.67 mg/kg; 60 kg person). The oral dose in the mouse study was 2 mg/kg/day; or 0.24-fold the maximum oral human dose, based on body surface area. The maximum IM daily dose is up to 120 mg/day (2 mg/kg; 60 kg person), for a safety margin of 0.08-fold, based on body surface area.

- Ketorolac was not carcinogenic in either rats given up to 5 mg/kg/day orally for 24 months or in mice given 2 mg/kg/day orally for 18 months. These doses are approximately 900-times and 300-times higher, respectively, than the typical human topical ophthalmic daily dose given as twice daily to an affected eye on a mg/kg basis (Acuvail® PI 2012).

  Note: According to the Acuvail® PI, the recommended dose of ketorolac was 0.45% BID. Assuming a 35 µL drop and 60 kg person, this dose corresponds to 5.25 µg/kg/day (unilateral dose).The safety margins are 30-fold and 155-fold the dose in mice and rats, respectively, based on body surface area.

- Ketorolac induced adenoma of adrenal cortex in a 2-year study in rats at a dose that was 7-fold higher than the maximum oral dose in humans and at a dose which was 7-fold higher than the maximum intramuscular dose in humans. Percentages of male rats with cortical adenoma were 6%, 14%, and 12% at 0.8, 2.0, and 5.0 mg/kg/day doses, respectively, and 4%, 10%, and 10% for female rats at the same doses. Five percent of male and female rats in the control group also showed cortical adenoma. The 0.8 mg/kg/day dose, which did not cause increased adenoma, corresponds to a C_{max} of 4870 ng/mL (assuming linear PK, per the Toradol® label [Toradol® PI 2007]). This represents an exposure multiple of at least 300-fold over the maximum measured KE exposure after OMS302 administration.

  Note: The source of the data showing an induction of adenoma is not clear to the reviewer as it is not found in the labels for the cited ketorolac products.

9 Reproductive and Developmental Toxicology

No reproductive or developmental toxicity studies were performed by the sponsor with OMS302 or with phenylephrine hydrochloride or ketorolac tromethamine.

Regarding phenylephrine hydrochloride, no formal regulatory-compliant reproductive toxicity studies have been conducted. The sponsor cited the published studies summarized in the National Toxicology Program report (Ref. 10 above). Phenylephrine given to pregnant rabbits during the last third of gestation produced fetal growth retardation and the onset of early labor (Shabanah, 1969). The use of medications containing phenylephrine during the first 4 months of pregnancy was associated with a greater than expected number of eye, ear, and other minor malformations in humans (Heinonen, 1977). Two other epidemiologic studies found no association between congenital disorders and use of phenylephrine during pregnancy (Jick, 1981; Colley, 1982). Para-sympathomimetic agents consistently caused external and cardiac malformations when administered to chick embryos, but phenylephrine did not cause similar defects (Hodach, 1975; Bruyere, 1983).

Regarding ketorolac tromethamine, the sponsor summarized the following information (note: this reviewer revised the exposure margins to be consistent with those in the approved labels):

COX-1 inhibition is associated with the disruption of heart development [Gupta 2003]. In rats, ketorolac increased the incidence of ventral septal defects [Cappon 2003]. Reproduction studies have been performed in rabbits using daily oral doses at 3.6 mg/kg and in rats at 10 mg/kg during organogenesis. Results of these studies did not reveal evidence of teratogenicity to the fetus. Oral doses of ketorolac tromethamine at 1.5 mg/kg, which was 0.14-times the human AUC, administered after gestation day 17 caused dystocia and higher pup mortality in rats (Toradol® label). Ketorolac tromethamine did not impair fertility when administered orally to male and female rats at doses up to 225-times and 400-times, respectively, the maximum recommended human topical ophthalmic dose, assuming 100% absorption in humans and animals (Acular® label). The exposures margins noted above for topical phenylephrine in Acular® label do not apply to the intraocular dose in OMS302.

According to clinical study # OMS302-ILR-004 conducted under this NDA, detectable phenylephrine plasma concentrations were observed in 1 of 14 subjects. The maximum concentration observed in this subject was 1.7 ng/mL, occurred after instillation of topical preoperative phenylephrine drops and prior to exposure to Omidria; lower values of 1.2 to 1.3 ng/mL were observed over the subsequent 2 hours. These concentrations (observed in only one subject) are comparable or below those reported after oral administration of a 10 mg dose or topical ocular administration of 2.5% or 10% phenylephrine drops (overall plasma level range of 0.65-24 ng/mL).

The sponsor is not including any reproductive data for phenylephrine in the proposed labeling. This is consistent with the labels for NDA 203-510 (Phenylephrine Hydrochloride Ophthalmic Solution 2.5% and 10%; approved on March 2013) and NDA 203-826 (Phenylephrine Hydrochloride IV Injection; approved on December 2012), both indicated for short-term use. Based on the expected low systemic exposure to phenylephrine, a similar label for the intended product is considered acceptable.

There were detectable ketorolac plasma concentrations in 10 of 14 subjects treated with Omidria (Study # OMS302-ILR-004). The maximum ketorolac concentration was 4.2 ng/mL (excluding one subject with a value of 15.2 ng/mL at 24 hrs – value believed to be spurious because it was higher than any value at previous timepoints). The maximum concentration of 4.2 ng/mL is lower than what is reported with 0.5% ketorolac eye drops (11 to 23 ng/mL), and more than 200-fold below the C_{max} reported after a single oral dose of Toradol® (870 ± 22 ng/mL; Toradol® label).

Regarding ketorolac, the sponsor adapted the wording in the Toradol® and Acular® (Ketorolac Tromethamine Ophthalmic Solution 0.5%; approved on Nov 1992) labels to the Omidria dose. Acular® is indicated for a 2-week treatment duration (one drop 4x/day) vs. the single dose in the current study; Toradol® (IV, IM, oral; first approved 1989) is indicated for acute pain in adult patients for a combined treatment duration of ≤5 days. The reviewer's suggested changes to the proposed Omidria label are shown below.

Sponsor' proposed label:

Pregnancy Category C - Animal reproduction studies have not been conducted with Omidria. It is also not known whether Omidria can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Omidria should be used in pregnant women only if clearly needed.

Ketorolac, administered during organogenesis, was not teratogenic in rabbits or rats at oral doses (b) (4) When administered to rats after Day 17 of gestation at oral doses (b) (4) .

(b) (4)

Reviewer's recommendations (changes are marked in italic font):

Pregnancy Category C - Animal reproduction studies have not been conducted with Omidria *or phenylephrine*. It is also not known whether Omidria can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Omidria should be used in pregnant women only if clearly needed.

Ketorolac, administered during organogenesis, was not teratogenic in rabbits or rats at oral doses (b) (4)

[redacted] 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 recommended human ophthalmic dose (RHOD), respectively. When administered to rats after Day 17 of gestation at oral doses up to [redacted] *.5 mg/kg/day (740-times the plasma exposure at the RHOD), ketorolac produced dystocia and increased pup mortality.*

[redacted]

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

The C_{max} values were extrapolated from the most conservative values reported in Mroszczak *et al*[11]. The most conservative value was defined as the lowest C_{max}/dose ratio. Therefore, the C_{max} values used to extrapolate the oral doses in the label were:

- Rat: 2084 ng/ml per mg/kg (using the reported C_{max} of 6.46 µg/mL at the 3.1 mg/kg dose)
- Rabbit: 1340 ng/ml per mg/kg (using the reported C_{max} of 1.34 µg/mL at the 1 mg/kg dose)

These extrapolations assumed a linear relationship between the reported oral doses and oral C_{max} values. The maximum plasma concentration of 4.2 ng/mL observed in patients treated with Omidria was used to calculate ketorolac exposure multiples (Table 10).

Table 10: Exposure Margins - Section 8.1 of Proposed Label

Dose	Estimated C_{max} (ng/mL)	Exposure Margins
Rat		
1.5 mg/kg	3,126	744
10 mg/kg	20,840	4,962
Rabbit		
3.6 mg/kg	4,824	1,149

[11] Mroszczak EJ *et al*., *Drug Metab Dispos*. 1987 Sep-Oct,15(5):618-626 (1987).

11 Integrated Summary and Safety Evaluation

OMS302 is a combination drug product containing 12.4 mg/mL phenylephrine hydrochloride and 4.24 mg/mL ketorolac tromethamine that is added to irrigation solution (e.g., balanced salt solution) for use during intraocular lens replacement procedures. OMS302 (4 mL) added to irrigation solution results in final concentrations of 480 µM phenylephrine hydrochloride and 89 µM ketorolac tromethamine. The intended use of OMS302 is for the (b) (4) prevention of intraoperative miosis during intraocular lens replacement, and the reduction of (b) (4) postoperative ocular pain.

Each of the active ingredients has been approved for topical ocular human use at higher concentrations than those in OMS302 but not for intracameral use (e.g., Phenylephrine Hydrochloride Ophthalmic Solution, 2.5% and 10% indicated for pupil dilation [up to 3 drops; up to 10.5 mg/eye]; ACULAR® 0.5% topical ophthalmic ketorolac tromethamine solution indicated for the treatment of inflammation following ocular surgery or temporary relief of ocular itching due to seasonal allergic conjunctivitis [1 drop 4x/day; 0.7 mg/eye/day]. For comparisons to approved topical ophthalmologic products, the final phenylephrine and ketorolac concentrations of 480 µM and 89 µM in OMS302 in the irrigant correspond to approximate concentrations of 0.0098% (w/v) and 0.0034% (w/v), respectively. However, on a mg basis, a higher amount of both APIs is delivered to the eye with OMS302, i.e., up to 49.6 mg phenylephrine hydrochloride (12.4 mg/mL x 4 mL) and up to 16.96 mg ketorolac tromethamine (4.24 mg/mL x 4 mL).

The ocular safety of the combination is supported by the results of the ocular toxicity study in African green monkeys (Study RX07.07). The NOAEL was the highest dose administered (7200 µM phenylephrine hydrochloride: 900 µM ketorolac tromethamine x 208 mL). The ocular exposure to phenylephrine and ketorolac at the NOAEL in ocular toxicology study # RX07.07 were, respectively, 7.2-fold and 4.2-fold above the maximum anticipated clinical exposures (Tables 10 and 11). Relative to the final concentrations of phenylephrine hydrochloride and ketorolac tromethamine in OMS302 intended for clinical use (480 µM phenylephrine hydrochloride: 89 µM ketorolac tromethamine), the NOAEL concentrations represent 15-fold and 10-fold higher multiples for phenylephrine and ketorolac, respectively. The absence of any test article-related findings in assessments of ocular physiology and histopathology supports the ocular safety of this product.

In Study RX07.07, there was no systemic toxicity based on clinical signs, body weights, food consumption, ECG, hematology, clinical chemistry, selected organ weights and urinalysis. Systemic tissue histopathology was not conducted. However, the systemic exposure of phenylephrine (Table 11) and ketorolac (Table 12) observed in the monkey was within the range of the levels observed in humans after administration of ocular phenylephrine drops (0.86-24 ng/mL; Table 11) or oral, intramuscular, or intravenous ketorolac (870-4650 ng/mL; Toradol® label). Therefore, it was not expected that these levels in the monkey would result in adverse findings.

Table 11: Comparison of Phenylephrine (PE) Exposure in Nonclinical and Clinical Ophthalmological Pharmacokinetic Studies

Study	N	PE Dose	Anterior Chamber or Topical Exposure (µmoles)	Plasma Concentration
RX07.07 - low	6 (nonclinical)	720 µM x 203 mL	146	6.9 ng/mL
RX07.07 - mid	6 (nonclinical)	2160 µM x 200 mL	432	9.2 ng/mL
RX07.07 - high	6 (nonclinical)	7200 µM x 208 mL	1500	38.3 ng/mL
OMS302-ILR-004	14	480 µM x 500mL	208	1.43 ng/mL*
Advil NDA 022113 2011	56	10 mg PO	NA	Mean C_{max} 0.65 ± 0.46 to 0.87 ± 0.58 ng/mL
Whitson 1993	13	10% x 30 uL x 2 drops	29.5	0.86 ng/mL
Kumar 1986	15	2.5% aqueous x 2 drops	12.3	3.15 ng/mL
Kumar 1985	13	2.5% x 2 drops	12.3	5.55 ng/mL
Kumar 1985	11	10 % x 2 drops	49.1	24 ng/mL
Chien 1985	1	2.5% x 2 drops	12.3	4 ng/mL
Chien 1985	1	10% x 2 drops	49.1	9 ng/mL

*This subject also had a value of 1.7 ng/mL at t = 0, presumably due to pre-operative use of PE-containing eye drops.

Table 12: Comparison of Ketorolac (KE) Exposure in Nonclinical and Clinical Ophthalmological Pharmacokinetic Studies

Study	N	KE Dose	Anterior Chamber or Topical Exposure (µmoles)	Highest KE Level Measured
RX07.07 - low	6 (nonclinical)	90 µM x 203 mL	18.3	47.9 ng/mL
RX07.07 - mid	6 (nonclinical)	270 µM x 200 mL	54	55.1 ng/mL
RX07.07 - high	6 (nonclinical)	900 µM x 208 mL	187	189.3 ng/mL
OMS302-ILR-004	14 (clinical)	89 µM x 500 mL[a]	44.5	4 ng/mL[b]
Acuvail PI 2012	26 (clinical)	13,328 µM x 1 drop x TID	2.0	11-23 ng/mL in 5 subjects: BLLOQ in 21 subjects

[a] Represents the maximum anticipated exposure if the entire dose of OMS302 is used.

[b] Excludes a value of of 15.2 ng/mL measured in one patient at 24 hour. This value was higher than any value at previous timepoints in this patient, hence is believed to be spurious.

The clinical PK of OMS302 was evaluated in 14 subjects in the Phase 3 trial OMS302-ILR-004. Plasma concentrations of phenylephrine were undetectable at all timepoints for all but one subject who received OMS302. The only subject with detectable phenylephrine had a value of 1.7 ng/mL at the pretreatment timepoint (presumably due to exposure to the preoperative phenylephrine 2.5% eye drops and not due to OMS302), and lower values of 1.2 to 1.3 ng/mL over the subsequent two hours. These levels are lower than those found in the published literature with clinical use of phenylephrine-containing eye drops (Table 11).

In Phase 3 trial OMS302-ILR-004, ketorolac was detected in 10 of 14 subjects treated with OMS302 and 1 of 12 subjects treated with placebo. The sponsor believes that ketorolac measured in some subjects at the 24-hour postsurgery timepoint may have been due to application of postoperative ketorolac ophthalmic eye drops scheduled to begin the day after surgery, e.g., the placebo-treated subject. The amount of ketorolac detected was low, in the 1 to 4 ng/mL range. These levels are lower than what is reported in the label for Acular® ketorolac 0.5% eye drops (11 to 23 ng/mL), and considerably lower than the average C_{max} reported in the label for Toradol® (870 ng/mL after a single 10 mg oral dose, 1140-4550 ng/mL after a single 15-60 mg intramuscular dose, and 2470-4650 ng/mL after a single 15-30 mg intravenous bolus).

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

The recommendations for the reproductive as well as carcinogenicity information in the proposed Omidria label are discussed under Sections 8 and 9 of this review, respectively.

Four potentially genotoxic impurities in the drug substance/drug product and several leachables/extractables from the glass vial and elastomeric stopper were detected, primarily under accelerated conditions. The levels observed are not expected to be of main toxicological concern for the proposed dose regimen.

Therefore, there are no nonclinical issues that will preclude the approval of Omidria.

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/s/

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