Phenylephrine 1%/Ketorolac 0.3% Injection (OMIDRIA)

Drug Monograph

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The purpose of VA PBM Services drug monographs is to provide a comprehensive drug review for making formulary decisions. Updates will be made when new clinical data warrant additional formulary discussion. Documents will be placed in the Archive section when the information is deemed to be no longer current.

Executive Summary

Efficacy	• Two phase 3 trials compared phenylephrine/ketorolac (PE/KE) to vehicle • The change in pupil diameter during surgery was 0.1mm and -0.5mm for PE/KE and vehicle respectively. • Approximately 9.8% of PE/KE and 43% of vehicle treated eyes had a pupil diameter <6mm at any time during surgery • Approximately 2% of PE/KE and 27% of vehicle treated eyes had pupil constriction ≥2.5mm at any time during surgery • Approximately 96% of PE/KE and 77% of vehicle treated eyes had a pupil diameter ≥6mm at cortical clean-up • Pain score using visual analog scale within 12 hours of surgery was 4.2 and 9 for PE/KE and vehicle respectively.
Safety	• Based on 459 patients who received PE/KE, the adverse event profile and tolerability of PE/KE was similar to vehicle
Other Considerations	• Preoperative mydriatics are still required • PE/KE must be diluted in 500mL of ophthalmic irrigation solution • Studies comparing PE/KE to standard practices are lacking

Introduction

During cataract surgery or intraocular lens replacement, adequate pupil dilation is needed to allow for visualization of the capsulorhexis and the lens, ease of instrument maneuvering, and decrease the risk of complications. Commonly, mydriatic agents (anticholinergic + sympathomimetic) are administered pre-operatively. Mydriatic agents are usually administered topically, but have also been administered intracamerally. Miosis during cataract surgery can occur and is thought to be due to increase in prostaglandin concentration. Non-steroidal anti-inflammatories (NSAIDs) have been added to the pre-operative regimen to enhance and prolong mydriasis.

FDA Approved Use

Phenylephrine/ketorolac (PE/KE) is added to an ophthalmic irrigation solution used during cataract surgery or intraocular lens replacement and is indicated for maintaining pupil size by preventing intraoperative miosis and reducing postoperative pain.

Current VA Alternatives

Mydriatics: atropine, cyclopentolate, homatropine, phenylephrine, scopolamine, tropicamide
NSAIDs: ketorolac, flurbiprofen

Dosage and Administration

- Must be diluted prior to intraocular use
- 4mL of phenylephrine/ketorolac is diluted in 500mL of ophthalmic irrigation solution.
- Irrigation solution is to be used as needed for the surgical procedure

How Supplied/Storage

Phenylephrine/ketorolac is supplied as a 4mL sterile solution containing 1% phenylephrine and 0.3% ketorolac in a single-patient-use vial. The undiluted solution is stored at 20°-25°C (68°-77°F). The storage period for the diluted product is no more than 4 hours at room temperature or 24 hours under refrigeration.

Efficacy

There are 4 randomized, double-blind clinical trials comparing PE/KE to the individual components or vehicle in patients undergoing intraocular lens replacement (**Table 1**). Only one trial been published at this time. Other information was obtained from poster presentations at scientific meeting, FDA meeting transcripts, and the product package insert. Limited data were available for the Phase 1 and 2 trials; therefore, the phase 3 trials (study 003 and study 004) will be the primary focus of this review.

Table 1: Phenylephrine/Ketorolac Clinical Trials

	Study 005 (n=61)	Study 001 (n=221)	Study 003 (n=402)	Study 004 (Lindstrom 2014) (n=406)
Phase	1/2	2	3	3
Treatment arms	PE/KE; PE; Vehicle	PE/KE; PE; KE; Vehicle	PE/KE; Vehicle	PE/KE; Vehicle
Follow-up	14 days	30 days	14 days	90 days

Abbreviations: KE=ketorolac; PE=phenylephrine

For the Phase 3 trials, patients were eligible if they were ≥ 18 years old, scheduled to undergo unilateral cataract extraction and lens replacement or refractive lens exchange with coaxial phacoemulcification device, BCVA of 20/400 or better in the non-study eye, and intraocular pressure between 5-22mmHg in the study eye.

Key exclusion criteria were hypersensitivity to any trial required medications, iritis, ocular trauma with iris damage, connective tissue disease, extraocular/intraocular inflammation in either eye, active ocular infection in either eye, chronic eye disease that could affect pupil dilation, pseudocapsular exfoliation, treatment with an alpha-blocking agent, narrow-angle or unstable glaucoma or glaucoma being treated with prostaglandins or prostaglandin analogs, use of NSAIDs, cyclosporine and /or mast cell stabilizers within 7 days of surgery, intraocular nonlaser surgery in study eye within 3 months or intraocular laser surgery in study eye within 30 days of surgery.

Preoperatively, all patients received topical phenylephrine 2.5%, tropicamide 1% and an anesthetic agent (lidocaine or tetracaine) administered 30, 15, and 5 minutes prior to surgery. In addition, all patients received a viscoelastic during surgery and topical moxifloxicin starting 3 days prior to surgery and continuing post-operatively. Beginning the day after surgery, all patients received topical ketorolac for at least 7 days and were discharged with oral acetaminophen for pain. Patients were randomized to PE/KE or vehicle, administered intraoperatively in the irrigation solution.

Randomization was stratified according to Lens Opacities Classification II nuclear grade category. The primary outcome for both studies was intraoperative pupil diameter. The trial by Lindstrom had post-operative pain as a co-primary endpoint (secondary endpoint in Study 003). Pupillary diameter was measured from video recordings captured during the procedure. Post-operative pain was measured using 0-100mm visual analog scale (VAS).

The 2 coprimary outcomes were: change in pupil diameter from just prior to initial incision to immediately following incision closure and early postoperative pain during first 12 hours after surgery.

Other outcomes (% patients) included:

- Absolute pupil diameter <6mm at any time during the procedure
- Absolute pupil diameter ≥6mm at cortical clean-up
- Pupil constriction ≥2.5mm any time during the procedure (represents approximately a 50% decrease in operative field loss)
- Moderate-severe pain (VAS≥40) at any time during the first 12 hours post-operatively
- Pain-free (VAS=0) during the first 12 hours post-operatively

Demographic characteristics include: mean age 68 years, 41% males, LOCS II grade low (N0, N1) 81%, LOCS II grade high (N2, N3) 19%, brown eyes 52%, blue eyes 28%, grey eyes 7%, other color eyes <12%.

Pupil Diameter

The change in pupil diameter during surgery was 0.1mm and -0.5mm for PE/KE and vehicle respectively. Compared to placebo, there were significantly fewer patients in the PE/KE groups who had a pupil diameter <6mm

and pupil constriction ≥2.5mm during surgery. Significantly more PE/KE treated eyes had a pupil diameter ≥6mm at cortical clean-up (**Table 2).** Approximately half the irrigation solution (mean ~250mLs) was used during surgery.

Post-Operative Ocular Pain

Pain scores using VAS were obtained 2, 4, 6, 8, and 10-12 hours post-surgery. The mean area under the curve (AUC) VAS score within 12 hours postoperatively was significantly lower with PE/KE than vehicle. Numerically, more patients in the PE/KE groups were pain-free (VAS=0) and fewer patients had moderate-severe pain (VAS≥40), compared to the vehicle groups; however, the differences were not significant. **Table 2**

Table 2: Efficacy Outcomes for Phase 3 Trials

	Study 003		Study 004 (Lindstrom)	
	PE/KE (n=201)	Vehicle (n=201)	PE/KE (n=202)	Vehicle (n=204)
Change in pupil diameter during surgery (mm)	0.1*	-0.5	0.1*	-0.5
Pupil diameter <6mm at any time during surgery (%pts)	10.3*	47.2	9.2*	38.0
Pupil diameter ≥6mm at cortical cleanup (%pts)	96.2*	77.2	95.9*	77.0
Pupil constriction ≥ 2.5mm at any time during surgery (%pts)	3.3*	27.8	1.0*	26.5
VAS score AUC over 12h	4.1*	9.2	4.3*	8.9
VAS=0 at all time points (%pts)	-	-	27.7	20.3
VAS≥40 at any time (%pts)	-	-	7.9	13.4

*Significant difference vs. placebo vehicle

Adverse Events (Safety Data)

Adverse event data are based on the phase 3 trials.

Deaths

One patient receiving PE/KE died. The cause of death was due to an unrelated industrial accident.

Other Serious Adverse Events

The incidence of serious adverse events was similar between groups. None of the events were considered to be treatment-related.

Tolerability

There was 1 patient receiving PE/KE that had an adverse event leading to withdrawal from the trial.

Table 3: Frequency of Adverse Events

	Treatments	n	Tx-emergent AE (%)	Tx-related AE (%)	Eye-related AE (%)	Tx-emergent SAE (%)	d/c study due to AE (%)	Fatal AE (%)
Study 003	PE/KE	201	77.6	10.4	74.6	0.5	0.5	0.5
	Vehicle	201	76.6	15.4	74.1	0.0	0.0	0.0
Lindstrom 2014	PE/KE	202	58.4	10.9	48.5	1.0	0.0	0.0
	Vehicle	204	70.1	14.2	59.8	1.0	0.0	0.0

Common Adverse Events

Adverse event data are from trials 001, 003, 004. The most commonly reported ocular adverse events (AEs) reported by ≥2% of patients are shown in **Table 4**.

Table 4: Adverse Events Reported by ≥2% of Patients

	PE/KE (%) (n=459)	Placebo (%) (n=462)
Anterior chamber inflammation	24	22
Increased intraocular pressure	4	3
Posterior capsule opacification	4	4
Eye irritation	2	1
Foreign body sensation in eyes	2	2

Data obtained from product package insert

Look-Alike/Sound-Alike

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Phenylephrine /ketorolac OPH irrigation soln	None	None	None	Phenylephrine/cyclopentolate OPH soln Ketorolac OPH soln Phenylephrine OPH soln
Omidria	None	None	None	Omnipred OPH soln

Sources: Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List)

Contraindications

Known hypersensitivity to any of the ingredients

Warnings and Precautions

- Systemic exposure to phenylephrine can cause elevated blood pressure
- There is a potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives and other NSAIDs. There have been reports of bronchospasm or exacerbation of asthma associated with the use of ketorolac in patients with a known hypersensitivity to aspirin/NSAIDs or a past medical history of asthma. Use phenylephrine/ketorolac with caution in patients who have previously exhibited sensitivities to these drugs.

Drug Interactions

None reported in package insert

Conclusions

PE/KE added to irrigation solution has been compared to vehicle (irrigation solution alone). All patients received mydriatic agents preoperatively; NSAIDs were not given as part of the preoperative drug regimen. In this setting, PE/KE maintained pupil size during surgery and decreased early postoperative pain (10-12 hours postoperatively) compared to vehicle.

Studies are needed comparing PE/KE to medications typically administered for cataract/IOL replacement surgery (e.g., NSAIDs given preoperatively) and in complicated cases (e.g., patients who have small pupils, hard nucleus, alpha-blocker use such as tamsulosin, long surgery time, etc.).

References

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FDA Medical Review Transcripts for Omidria
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/205388Orig1s000MedR.pdf

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June 2015