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A NEW STANDARD FOR CATARACT SURGERY

BY STEPHEN LANE, MD, AND JOHNNY GAYTON, MD

Visualization during cataract surgery—the ability to see the surgical field clearly and to maneuver throughout the anterior chamber during the procedure—is easily understood as a crucial component of assuring a safe outcome for the patient. In many cases, the pupil remains adequately dilated so that the surgeon's view is not hampered; however, some pupillary constriction is inevitable in almost all cases and, in some instances, the decrease in pupil diameter becomes problematic for visualization, increasing the possibility of damaging the iris or other ocular structures with the surgical instrumentation.

Cataract surgery has advanced to the point where intraoperative complications are an infrequent occurrence; yet certain aspects, such as the degree to which the pupil constricts, remain unpredictable. To date, standard of care for minimizing this potentiality has been the application of topical nonsteroidal anti-inflammatory drugs (NSAIDs) in the preoperative period. This strategy relies on patients' compliance, and emerging evidence suggests that it is less than optimal for providing mydriasis or for preventing miosis (*see "NSAID Levels in the Anterior Chamber Before and After Cataract Surgery" on page 7*). Other strategies involve the off-label use of pharmacologic products that are often compounded.

With the recent availability of OMIDRIA (phenylephrine and ketorolac injection) 1% / 0.3%, there is a US Food and Drug Administration (FDA)-approved option for maintaining the pupil's diameter during cataract surgery. This product has a strong scientific rationale with proven efficacy in clinical trials. The phenylephrine component, as an α-1-selective adrenergic agonist, maintains mydriasis. The presence of the non-selective NSAID ketorolac has two functions through its prostaglandin inhibition: (1) prevention of miosis and (2) reduction of patient-reported postoperative pain, another unpredictable variable in cataract surgery. All three activities of OMIDRIA were demonstrated in clinical trials, leading to its approval by the FDA with the dual indication for maintenance of pupil size by preventing miosis and for reducing postoperative ocular pain.

Being an FDA-approved product means that OMIDRIA is also manufactured to rigorous industry standards, so surgeons can be assured of the potency, purity, sterility, and dosing consistency in every vial. This also means that surgeons can be less reliant on compounded and off-label use of products that are traditionally administered to prevent intraoperative miosis. Furthermore, because OMIDRIA is added to the balanced salt solution used for irrigation during the surgery, it provides steady-state concentrations in the eye throughout the case, preemptively inhibiting both miosis and postoperative pain.

The patient benefits of OMIDRIA are the primary aspects that should be considered by surgeons who might be interested in using this product. In addition, OMIDRIA has been granted pass-through status by the Centers for Medicare & Medicaid Services (CMS), and so there are some important considerations on the business side of things—both in the short-term and for the future of cataract surgery—that bear mentioning (*see "What Is Pass Through? A Billing Perspective" on page 8*).

Below we will offer some additional thoughts on the benefits of incorporating OMIDRIA into the surgical protocol, with some further perspectives on the administrative, business, and billing benefits that OMIDRIA provides. ■

The Scientific Rationale for OMIDRIA

By Stephen Lane, MD

The presence of phenylephrine in the OMIDRIA (phenylephrine and ketorolac injection) 1% / 0.3% formulation maintains pupil dilation. Eye surgeons are certainly familiar with its use as a dilation agent for patients undergoing a clinical eye examination. From a pharmacologic standpoint, as an α-1-selective adrenergic agonist, phenylephrine maintains mydriasis in cataract surgery, allowing for a larger window through which the surgeon can operate. When it is combined with ketorolac (both components contained in OMIDRIA), it becomes more effective than either agent alone or vehicle, as demonstrated with statistical significance in a four-armed (OMIDRIA vs. phenylephrine, ketorolac, and vehicle) Phase 2b clinical trial[1] in which all patients across all four groups received standard topical mydriatic and anesthetic medications preoperatively (Figure 1).

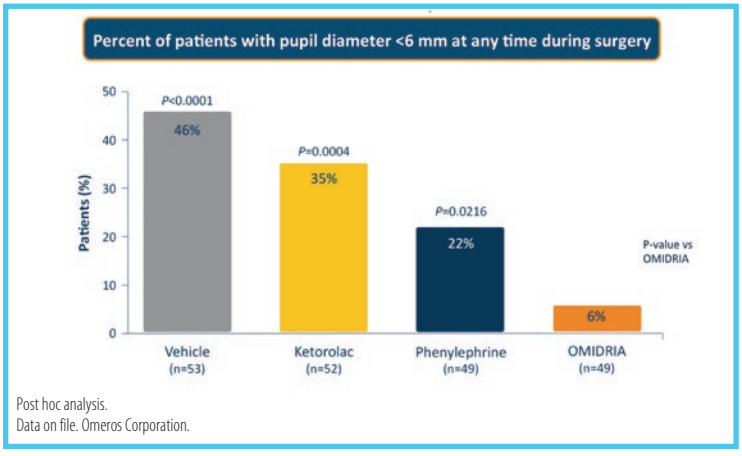

Figure 1. Percent of patients with pupil diameter <6 mm at any time during surgery in the Phase 2b study.

REVIEWING THE DATA

There is a growing body of literature demonstrating the safety and efficacy of OMIDRIA.

The Phase 3 clinical studies for OMIDRIA enrolled 808 adult patients undergoing cataract surgery or intraocular lens replacement in two randomized, multicenter, double-masked, placebo-controlled clinical trials. Pupil diameter was measured throughout the surgical procedure and postoperative pain was evaluated by self-administered 0-100 mm visual analog scale (VAS). All primary endpoints were met with statistical significance.[2]

Notably, 23% of placebo-treated subjects and 4% of OMIDRIA-treated subjects had a pupil diameter <6 mm ($p < 0.0001$) at the start of lens implantation (Figure 2).[1,3] Importantly, the data demonstrated that dilation of the pupil was consistent across the entirety of the procedure with the OMIDRIA-treated patients having more than a 4-fold decrease in the incidence of pupil diameter <6 mm at any time point during surgery when compared to placebo-treated patients (Figure 3).

OMIDRIA also outperformed placebo on pain reduction (Figure 4). In the 10 to 12 hours after the procedure, 26% of OMIDRIA-treated subjects reported no pain compared with 17% in the placebo group ($p = 0.0014$) and twice as many placebo-treated patients had moderate-to-severe pain (i.e., VAS ≥40) despite 40% more patients in the placebo group than in the OMIDRIA group using analgesics on the day of surgery.[2]

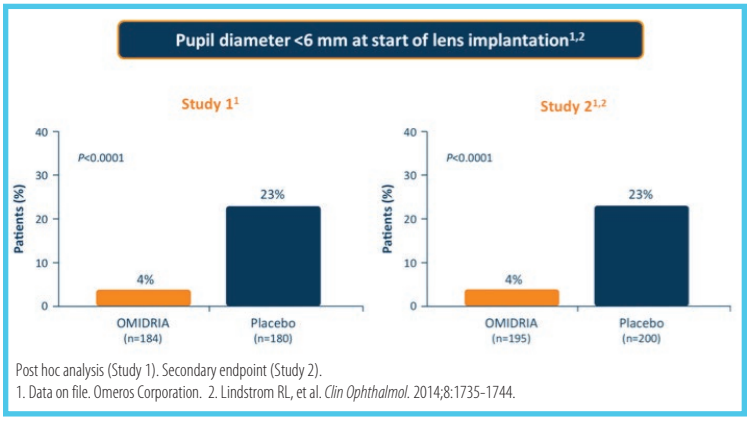

Figure 2. Pupil diameter <6 mm at start of lens implantation.

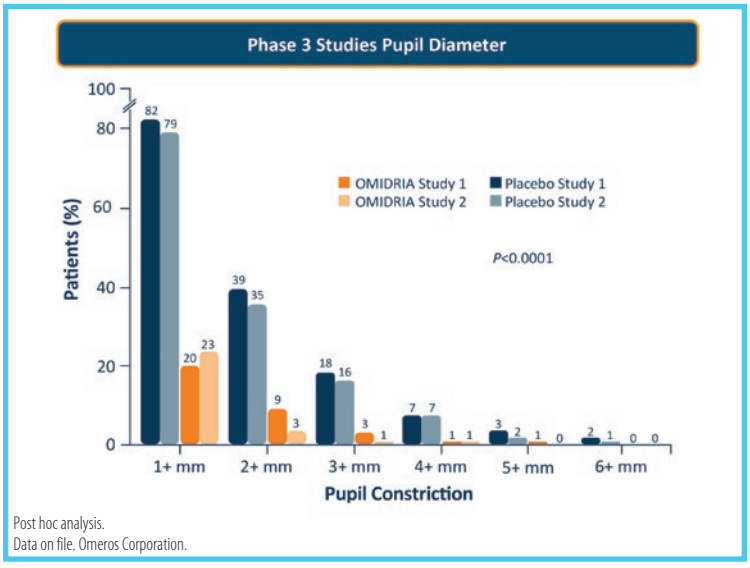

Figure 3. Intraoperative pupil constriction at any time during surgery in the Phase 3 studies.

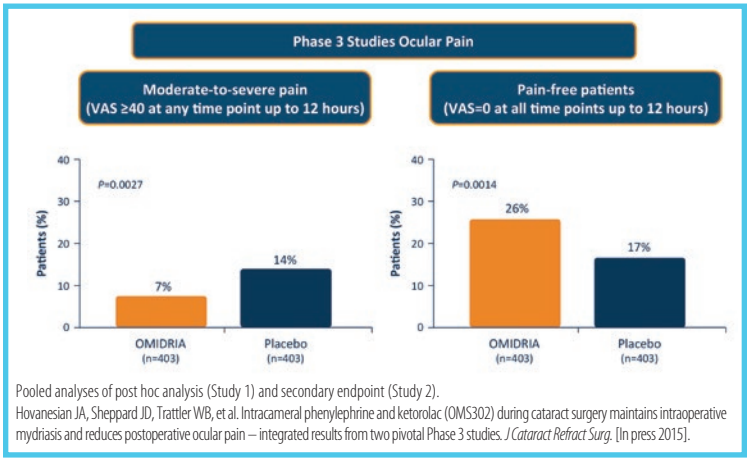

Figure 4. Ocular pain outcomes in the Phase 3 studies.

As in the Phase 2b trial, all patients in both groups in each of the Phase 3 trials received standard topical mydriatic and anesthetic medications preoperatively, so the differences between the OMIDRIA and the placebo groups seen in pupil diameter and pain are on top of effects from standard preoperative drops. The drug was safe and well tolerated in these studies; the rates of adverse reactions were similar to placebo

Please see Full Prescribing Information on pages 11 and 12.

THE VALUE OF PASS-THROUGH STATUS FOR THE FACILITY

By Candace S. Simerson

OMIDRIA (phenylephrine and ketorolac injection) 1% / 0.3% is the first and only product approved by the US FDA for maintaining pupil size and reducing postoperative pain. Following its approval, OMIDRIA was granted pass-through status by CMS, meaning that CMS will provide reimbursement above and beyond the prospective payment rate for use of the product when it is billed as a supply through the facility. This designation was awarded and became effective on January 1, 2015 and will last through December 31, 2017.

Pass-through status has several potential benefits. Practically speaking, because OMIDRIA is reimbursed at the Average Selling Price plus 6%, surgeons are provided a low-risk opportunity to try it in their facility and make their own determination about its usability, practicality, and applicability to their surgical regimen. It should be noted that pass-through status should not have any impact on cost reporting metrics; at Minnesota Eye, we have not experienced any issues with CMS related to billing or payment for the use of OMIDRIA.

Currently, pass-through status applies to all patients for whom Medicare is the primary carrier (facilities should confirm payment policies for Medicare Advantage and commercial plans in advance to ensure coverage). Most other payers can be encouraged to review their policies regarding new technologies to follow CMS' lead with regard to payment policies. In our center, we are proactive with other carriers when inquiring about coverage by providing education and written documentation about CMS pass-through status for the use of OMIDRIA. A good opportunity to do this might be at the time of contract renewal; however, if coverage benefits have not been defined and a patient is determined to be a good candidate, facilities can ask patients to follow up with their individual carriers to inquire about their benefits, which can help build momentum for when the facility discusses contracts with those payers.

Above and beyond the financial implications of adding OMIDRIA to a facility, it has proven benefits for preventing miosis and reducing postoperative pain, which may translate to patients' outcomes and their perceptions of their respective surgical experience. As health care continues to evolve toward a value-based reimbursement model, an increasing emphasis will be placed on patients' outcomes and experiences. If patients are able to avoid complications and any unnecessary discomfort or ocular pain, memories of their surgery are more likely to be positive, resulting in better ratings on subsequent surveys, online reviews, or when recalling the event to friends or family. ■

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Phase 3 Safety Treatment Emergent Adverse Events

AEs Occurring in ≥2% of Patients Overall in the Two Phase 3 Studies	OMIDRIA (n=403) n (%)	Placebo (n=405) n (%)
Any event	242 (60.0)	271 (66.9)
Eye pain	122 (30.3)	162 (40.0)
Eye inflammation	63 (15.6)	62 (15.3)
Anterior chamber inflammation	36 (8.9)	34 (8.4)
Headache	26 (6.5)	38 (9.4)
Intraocular pressure increased	19 (4.7)	14 (3.5)
Posterior capsule opacification	18 (4.5)	15 (3.7)
Ocular discomfort	12 (3.0)	21 (5.2)
Photophobia	12 (3.0)	20 (4.9)
Corneal edema	11 (2.7)	12 (3.0)
Vision blurred	5 (1.2)	17 (4.2)
Conjunctival hyperemia	11 (2.7)	10 (2.5)
Foreign body sensation in eyes	8 (2.0)	10 (2.5)

Pooled data.

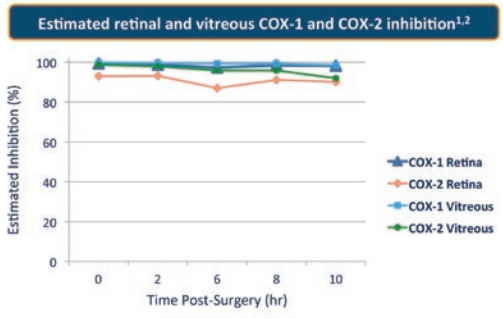
Hovanesian JA, Sheppard JD, Trattler WB, et al. Intracameral phenylephrine and ketorolac (OMS302) during cataract surgery maintains intraoperative mydriasis and reduces postoperative ocular pain – integrated results from two pivotal Phase 3 studies. *J Cataract Refract Surg*. In press 2015.

Figure 5. Treatment-emergent adverse events in the Phase 3 studies.

(Figure 5), and there were no treatment-related serious adverse events.

These data certainly make sense from a biologic standpoint, as phenylephrine is highly selective for the receptors that maintain pupil size, and, from a pharmacologic standpoint, phenylephrine is more selective than epinephrine, an agent which is sometimes added to the irrigation solution for mydriasis. In the eye, both phenylephrine and epinephrine are mydriatic agents only. In fact, OMIDRIA was approximately 4-fold better than phenylephrine alone at preventing pupil size <6 mm[1]—a difference resulting from the prostaglandin-inhibiting effect of ketorolac in OMIDRIA.

There is additional biologic rationale provided by a canine study in which OMIDRIA-containing irrigation solution was used during conventional phacoemulsification and lens replacement.[4] In the study, it was shown that OMIDRIA maintained ketorolac levels throughout ocular structures (i.e., retina, cornea, sclera, vitreous, choroid, lens capsule, ciliary body, and iris) that effectively ablate COX-1 and COX-2 for at least 10 hours postoperatively (the longest timepoint measured). The significance is that COX-1 and -2 are important mediators in the inflammatory cascade, and blocking them prevents downstream activity, namely the release of prostaglandins that in turn cause the release of other activators of inflammation. That the ketorolac remained hours after OMIDRIA was irrigated in the eye in the canine study suggests a durable treatment effect that may have important implications for reducing postoperative pain. In fact, as noted above, clinical trials



1. Florio V, Cowan L, Prusakiewicz JJ, Bentley E, Waterbury, LD. Ocular tissue distribution of ketorolac after administration of OMS302 to dogs during IOL replacement. Electronic poster session presented at: American Society of Cataract and Refractive Surgery. 2015 ASCRS-ASOA Symposium and Congress; 2015 April 17-21; San Diego, CA. 2. Waterbury LD, et al. *Curr Med Res Opin*. 2006;22:1133-1140.

Figure 6. Estimated retinal and vitreous COX-1 and COX-2 inhibition in the canine study of OMIDRIA. In the study, Ketorolac levels inhibited COX-1 and COX-2 pathways from 0 to at least 10 hours, consistent with Phase 3 pain data.

showed that postoperative pain was significantly lower in the first 10 to 12 hours in the OMIDRIA (phenylephrine and ketorolac injection) 1% / 0.3% group (Figure 4).[2]

Although not yet examined in humans, the dog data noted above show the extended duration of prostaglandin-inhibiting activity in the retina and in other intraocular structures. Additional studies still need to be done, but there is certainly biologic plausibility to believe that OMIDRIA could be effective in addressing retinal inflammation.

MY EXPERIENCE WITH OMIDRIA

My experience with OMIDRIA in the OR reflects the strength of the data shown in the clinical trials and also applies to certain situations in cataract surgery where the pupil tends to constrict during the procedure, such as pseudoexfoliation and floppy iris syndrome (IFIS). Previously, these are patients in whom I have sometimes had to use pupil expanding devices and are additional scenarios in which I have found OMIDRIA to be extremely helpful. Moreover, when used across routine to complex cases, the ability to maintain pupillary dilation throughout the procedure is clear and I get fewer reports of pain from patients.

I have found OMIDRIA to be particularly beneficial for femtosecond laser-assisted cataract surgery. The cavitation bubbles created by the laser can irritate the pupil and cause constriction; when OMIDRIA is on board, the pupil comes right back. I have actually modified my use of OMIDRIA in these cases: I inject about 5 cc of OMIDRIA-containing irrigation solution into the eye at the beginning of the procedure before starting irrigation/aspiration (I/A). That way, I am confident that the pupil will not constrict as I perform manipulations in the anterior chamber before I start irrigation and gives me a "head start" on maintaining pupillary mydriasis.

PASS-THROUGH STATUS

The clinical trial data leave little doubt as to the efficacy and safety of OMIDRIA. The salient question about whether it makes sense in practice is cost: Does OMIDRIA make sense from a financial standpoint?

A drug like OMIDRIA would usually be covered by Medicare, and likely other payers, as part of the bundled payment for the surgical procedure. However, given the clear benefits of OMIDRIA, it is important that there not be barriers to its trial and adoption. We are fortunate that Congress passed, and CMS is implementing, the pass-through regulation, creating a pool of money available to all of medicine to facilitate the use of efficacious and innovative FDA-approved products that have received transitional pass-through status (*see "The Value of Pass-Through Status for the Facility on page 3*).

Importantly, pass-through funding is not money that is taken away from other Medicare beneficiaries, and the use of products with pass-through status does not affect payments to surgeons now or in the future. These are funds that have been specifically set aside by Congress and administered by Medicare for the sole purpose of fostering innovative new products to improve the quality of care delivered.

Pass-through, however, has a limited 24- to 36-month time window for each product awarded that status and, for OMIDRIA, pass-through status expires on December 31, 2017. Based on the amount of usage of OMIDRIA in the meantime, CMS will make a final determination as to whether OMIDRIA should be added to the bundled ambulatory payment classification for cataract surgery procedures; if it is, reimbursement will be adjusted upward accordingly. And so, the use of OMIDRIA today may have important implications on facility fees in the future.

CONCLUSION

The strategies that are popularly used to maintain pupil size involve off-label use of FDA-approved products as well as use of non-FDA-approved compounded products. Surgeons may be taking a risk if they continue to use approved products in an off-label manner or non-approved agents for this indication. For, if a complication occurs under those conditions, it may be difficult to justify the use of one or more of them when an FDA-approved product is available. With OMIDRIA, we have an FDA-approved product to prevent miosis, plus the added benefit of reducing postoperative pain. The drug works in both routine and complex cases, and I have noticed real benefits across my practice and my patients. Additionally, the opportunities provided by pass-through allow me to do what is good for my patients without affecting the cost structure of my facility. ■

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1. Omeros data on file.
2. Hovanesian JA, Sheppard JD, Trattler WB, et al. Intracameral phenylephrine and ketorolac (OMS302) during cataract surgery maintains intraoperative mydriasis and reduces postoperative ocular pain – integrated results from two pivotal Phase 3 studies. *J Cataract Refract Surg*. In press 2015.
3. Lindstrom RL, et al. *Clin Ophthalmol.* 2014;8:1735–1744.
4. Florio V, Cowan L, Prusakiewicz JJ, Bentley E, Waterbury, LD. Ocular tissue distribution of ketorolac after administration of OMS302 to dogs during IOL replacement. Electronic poster session presented at: *American Society of Cataract and Refractive Surgery*. 2015 ASCRS-ASOA Symposium and Congress; 2015 April 17–21; San Diego, CA.

OMIDRIA: Good For Patients and Good for the Surgeon

By Johnny Gayton, MD

I was involved in some of the first studies looking at the use of non-steroidal agents for the prevention of miosis many years ago, and I have since been a big believer in their role during cataract surgery. However, I have long had a belief that we could do better in terms of keeping the active drug in the eye longer, throughout the entirety of the case, and perhaps even into the postoperative period to have a beneficial effect on postoperative pain.

When I was able to get OMIDRIA and use it during my surgeries, I immediately saw the benefits of it. To date, because I have incorporated the product into most cataract procedures that I perform, I have not had to use a Malyugin ring in a case in which I used OMIDRIA. And I say that having used OMIDRIA in both routine and some very difficult cases (*see "The Proof is in the Results" on page 5*).

OMIDRIA-ASSISTED CATARACT SURGERY: MORE THAN JUST A NAME

Having phenylephrine and ketorolac present in the anterior chamber throughout cataract surgery is of tremendous benefit, so much so that I now inject a little of the balanced salt solution containing OMIDRIA directly into the sideport incision at the start of every case in which I intend to use it. I have found that this step decreases pain and frequently results in additional pupillary dilation. I also use this same solution to irrigate the cornea throughout the case. I directly inject the OMIDRIA solution a second time when I hydrodissect the lens. Of course OMIDRIA

THE PROOF IS IN THE RESULTS

By Lisa Barker, RN

As a nurse, I am conditioned to be skeptical about any new medication that comes to the marketplace. The surgeon I work for, Johnny Gayton, MD, is very innovative and on the cutting edge about using new technologies in surgery, and so I have seen a lot of products come to the market offering big promises, only to fall far short on what they deliver.

We have tried several strategies to maintain pupil dilation at our center, and this is especially important for patients with floppy iris syndrome and other conditions that confer a higher risk for miosis. In truth, we never settled on any particular strategy because a lot of the options, including the devices designed to mechanically hold the pupil open, may not be effective and may cause complications.

Naturally, then, when Dr. Gayton approached our staff with the idea of using OMIDRIA (phenylephrine and ketorolac injection) 1% / 0.3%, the only product approved by the FDA for addition to the irrigation to prevent miosis and to reduce postoperative pain, I was not expecting much.

However, during the first couple of cases, I started to see a difference in how the pupil responded during surgery. The benefit of OMIDRIA really was driven home to me when Dr. Gayton operated on a patient over 90 years old who had floppy iris syndrome and a 4+ cataract. This is exactly the kind of case in which we traditionally used a Malyugin ring. However, in this instance, we used OMIDRIA and, not only did we avoid the use of a Malyugin ring, Dr. Gayton was in and out of the eye in under 10 minutes, with absolutely no untoward events. The pupil remained dilated the entire time, and the pupil actually looked larger at the end of the case than when we started.

We had some initial miscues with the billing of OMIDRIA, but our staff has since worked through those issues. And now we have expanded our use of OMIDRIA during cataract surgery to include almost every patient whose insurance covers it. We have not had to use a Malyugin ring or other pupil-expanding device in any case in which we have incorporated OMIDRIA into the irrigation solution.

The introduction of OMIDRIA has necessitated an adjustment to our center's protocol, but it has not required much change in our OR routine. We have our front desk staff affix a sticker to each chart of patients who are eligible for OMIDRIA.

At our center, we have used OMIDRIA in about 50 to 60 cases. While we have not conducted a controlled clinical trial at our facility to assess the magnitude of the benefits OMIDRIA provides, I personally am no longer skeptical about its utility. I have noticed a real difference in pupil size in cases in which OMIDRIA is incorporated into the irrigation solution, as well as in Dr. Gayton's ability to get into and out of the eye in a safe and efficient manner. ■

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is then continuously irrigated during the phacoemulsification and IA parts of the procedure. Finally, I irrigate the capsular bag and anterior chamber with balanced salt solution containing OMIDRIA after lens implantation. The purpose of this irrigation is to decrease the risk of leaving any cataractous material in the eye. I believe that the additional intracameral ketorolac at the end of the case further decreases postop pain.

I have started to use the expression *OMIDRIA-Assisted Cataract Surgery* for cases in which I use the drug. Admittedly, I have borrowed that from the more commonly known *Femtosecond-Assisted Cataract Surgery* (FACS). I have also started using the term "OMIDRIA and Femtosecond-Assisted Cataract Surgery" (OFACS) in cases in which I use both. Not only does the pupil need to be dilated for the femtosecond laser to perform the capsulorrhexis and nuclear fracture, but that pupillary dilation needs to be maintained during the rest of the procedure to avoid complications and ensure accurate lens implantation. I take femto patients with 7 mm or smaller pupils to the OR for irrigation of balanced salt solution containing OMIDRIA into the anterior chamber through a self sealing sideport incision. I hydrate the incision with the same solution. The patient is then taken to the laser room for the femto procedure. I have seen no patient's pupil decrease in size when OMIDRIA was used prior to the femtosecond laser. No doubt this is in large part due to the early, effective block of prostaglandin production by the ketorolac component of OMIDRIA. The rest of the case is completed in the OR using balanced salt solution containing OMIDRIA.

This protocol recently became extremely relevant for a patient in my center undergoing a second eye cataract procedure. During the first eye surgery in which OMIDRIA was not available, at the start of the case the pupil immediately decreased in diameter to about 2.0 mm, leading me to use a Malyugin ring. Unfortunately, that left the pupil permanently stretched. There was also significant postoperative inflammation after the 45-minute long surgery. For the second eye, using OFACS, the pupil did not decrease, there was no need to use a Malyugin ring, and the operation took a total of 6 minutes. Needless to say, both the patient and the surgeon were absolutely thrilled with the result of the second procedure.

RESULTS IN THE OR

One of the aspects of OMIDRIA that I find particularly advantageous is the fact that it is fully FDA-approved for prevention of miosis and reduction of postoperative pain. The state of Georgia, where I practice, has some of the toughest regulations about compounding. Before OMIDRIA, I could not get a local pharmacy to compound Shugarcaine, and so my only options were to not use it at all during the surgery, or else make my own in my facility—a practice that is actually illegal in my home state. With the availability of OMIDRIA, I now have a drug produced under Good Manufacturing Practices (GMPs), assuring sterility and the correct concentration with every vial (see "*The Value of Using FDA-Approved Products in the Facility" on page 6*).

In our practice, after diluting OMIDRIA in the irrigation solution, we are using it three times before we get to the phacoemulsification stage of the procedure. That is why I believe that we are getting such impressive benefits on the prevention of pupil constriction and on pain control.

To date I have not had to use any Malyugin rings or perform a vitrectomy in an OMIDRIA case. Any bit of pupil dilation makes surgery safer and easier. Just a little bit of difference in pupil diameter can mean

THE VALUE OF USING FDA-APPROVED PRODUCTS IN THE FACILITY

By Robert B. Nelson, PA-C

Anything we can do at our facility to ensure compliance with good standards and practices is good for business—but more importantly, it's good for patient care.

When we consider incorporating new technology, devices, and pharmaceutical products in our facility, we try and gather as much information as possible so that we can make an informed decision about its merits. When several of our surgeons recently approached our facility's leadership about adding OMIDRIA (phenylephrine and ketorolac injection) 1% / 0.3% to the formulary, the fact that it had already gained approval from the US Food and Drug Administration and that it is manufactured to meet rigorous regulatory and manufacturing standards served as very important factors in our deliberations.

As in most centers, in the past our surgeons have used unapproved compounded products or have used approved products in an off-label fashion for the prevention of intraoperative miosis. Although largely successful in doing so, compounded pharmaceuticals do carry risks, both in terms of the supply chain and for patients' safety. In my opinion, anytime an FDA-approved medication can be used in place of a compounded agent, you have mitigated against risk, you have provided the patient with a product with proven safety and efficacy, and you have lowered your risk of criticism in the event of an untoward clinical outcome.

We were very early adopters of OMIDRIA because several surgeons in our facility were interested in replacing the use of compounded and off-label products in their surgical protocols. Over the 4 to 5 months we have had OMIDRIA available at our facility, our experience has been very good. Our surgeons are pleased with its efficacy and have the comfort of knowing that it is an FDA-approved medication which is manufactured to rigorous FDA standards.

Another factor that appealed to us about OMIDRIA is that it has gained pass-through status, which is a reimbursement category created by the Centers for Medicare & Medicaid Services for new technologies and products that may be used during a procedure or in a patient interaction and are reimbursed separately from the associated bundled facility payment. It is meant to encourage and foster innovation of new medications and devices. I think it is quite interesting that this payment designation has come up for discussion during several recent Congressional budget debates, yet this reimbursement line item has been left intact. Clearly, our political leaders see the value of fostering medical innovation to develop products that can have an impact on high-quality care while at the same time helping to reduce cost.

With respect to the healthcare system, the pass-through regulation is budget neutral—the funds for pass-through products are set aside annually by Congress and manufacturers across all specialties can access those funds for their respective products. If companies that innovate for ophthalmology don't avail themselves of this process to bring new products to market, then those funds are simply lost to other specialties. OMIDRIA, like other pass-through products, is reimbursed by Medicare at Average Selling Price plus 6% to cover administrative costs. Medicare Advantage and commercial payers are following suit, although coverage should be confirmed before using OMIDRIA in cataract surgery performed on beneficiaries of those insurance programs. Our experience so far with billing for OMIDRIA has been very encouraging. Medicare primary has reimbursed every one of our claims, and balances are being picked up by secondary carriers. With the pass-through reimbursement process, instead of costing us money to integrate this important new technology into practice, we can be fully reimbursed while giving our surgeons a chance to see for themselves if OMIDRIA is beneficial. How many other medications or devices end up being cost neutral to our centers? Adoption at our center started with only a few surgeons, but it wasn't long before OMIDRIA took its place as a new standard of care in our facility. The majority of our 35 or so surgeons now write orders for OMIDRIA.

Among the many things we discussed before moving forward with adding OMIDRIA to our formulary was the fact that adding it to the irrigation solution per the FDA-approved labeling, unlike using compounded medications and off-label use of approved products, OMIDRIA will not be not subject to citation by accrediting or state licensing bodies for the facility. This factor gave us confidence that we would comply with the good practices and standards of the various regulatory and governing bodies and accreditation organizations, which regularly survey our facility. Because OMIDRIA is fully FDA-approved as an additive to balanced salt solution of any kind, we know that by using it the chance of being criticized or subject to citation for using a compounded or off-label product in the irrigation solution to prevent miosis has been virtually eliminated. And that should be a comfort to all ASCs! ■

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the difference between a complication and not having a complication. That is to say, visualization is key in cataract surgery, and concern regarding complications and quality of care is on the rise. It is interesting to note that ProPublica has established a Surgeon Scorecard and associated website to report complication rates by surgeon and/or by facility for commonly performed elective procedures. Cataract surgery is not yet included, but ProPublica has initially focused on procedures with low complication rates, like cataract surgery, and an only 0.1% increase moves the risk label for the surgeon or facility from "low" to "medium" or "medium" to "high."

My previous mention of the Malyugin ring may suggest that I only consider OMIDRIA in complex cases, although that is not the case at all. In fact, I have used it in the vast majority of people for whom it is approved and who have insurance for it. Honestly I have even used it in some high risk patients who do not have insurance, and I have paid for it myself.

CONCLUSION

I have been performing cataract surgery for a long time, and I am a fan of anything that improves the procedure. The bottom line is that OMIDRIA does just that. I have little doubt that any surgeon who incorporates OMIDRIA into their surgical protocol will immediately see the many benefits it provides. ■

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NSAID LEVELS IN THE ANTERIOR CHAMBER BEFORE AND AFTER CATARACT SURGERY

BY DOUG KATSEV, MD

Some degree of miosis occurs with every cataract procedure, but the degree to which it affects the ability to perform intraoperative maneuvers is highly unpredictable and variable. For instance, a constriction of 1.0 mm is much more likely to be an issue in an eye with a pupil size of 4.0 mm versus one that is 6.0 mm. Because miosis is not predictable and will vary from patient to patient, it is incumbent on the surgeon to devise a strategy to mitigate the risk of intraoperative miosis.

I was involved in a study almost 25 years ago demonstrating that the presurgical topical application of NSAIDs reduces miosis.[1] However, results of a more recent experiment suggest that an approach to ensuring consistent delivery of a nonsteroidal agent during surgery may be needed.

STUDY RESULTS

I decided to measure the level of NSAIDs, following topical administration preoperatively, in the anterior chamber (AC) at the beginning of surgery and again at the end, after placement of the IOL. My assumption was that the combined effect of intraoperative maneuvers, including use of balanced salt solution during the case, would leave very little NSAID quantity at the conclusion of the case.

We enrolled 14 patients at my center for this demonstration study. Patients were instructed to use a topical ketorolac tromethamine formulation beginning the day prior to surgery and continuing on the day of surgery before operation. Immediately prior to the initial surgical incision, 100 µL of aqueous humor were drawn from the operative eye with a 30-gauge tuberculin syringe; after cataract extraction and placement of the IOL, another 100 µL of fluid were withdrawn from the AC. Samples were sent to an independent laboratory for analysis.[2]

Compliance with the preoperative regimen was relatively high, with 13 of 14 subjects using four doses of ketorolac the day prior to surgery as instructed, and one subject using three doses the day prior to surgery. All 14 subjects received topical ketorolac in the surgery center on the day of surgery. The initial draw of AC fluid was inadvertently skipped for two patients on the day of surgery, leaving 12 evaluable patients for the study.

Among our patients, the preoperative level of ketorolac ranged from 4.9 to 369 ng/mL; however, at the end of the surgery, samples ranged from less than 1.0 ng/mL to 6.32 ng/mL with eight of the 12 evaluable patients having ketorolac levels that were below the lower limits of quantification (LLOQ = 1 ng/mL).[2]

Preoperative Topical Medication Is Washed Out by Irrigation Solution

Patient	Prior to Incision (ng/mL)	Prior to Wound Closure (ng/mL)
1	87.4	Undetectable
3	39	Undetectable
4	4.9	Undetectable
6	195	Undetectable
7	29.5	1.80
8	75.1	6.32
9	369	2.11
10	105	Undetectable
11	244	2.90
12	64.6	Undetectable
13	137	Undetectable
14	120	Undetectable

Undetectable = below the lower limit of quantification (i.e., <1 ng/mL).

Katsev D, Katsev C, Pinnow J. Intracameral Ketorolac Concentration After Topical Ketorolac Administration Prior to Cataract Surgery. Electronic poster session presented at: American Society of Cataract and Refractive Surgery. 2015 ASCRS-ASOA Symposium and Congress; 2015 Apr 17-21; San Diego, CA. Study sponsored by Omeros Corporation.

Figure 7. Ketorolac levels in the anterior chamber at the start and end of cataract surgery.

IMPLICATIONS AND ANALYSIS

There is no set benchmark for how much NSAID should be in the eye at the start of surgery to reduce or eliminate the risk of miosis. However, it is reasonable to assume that it is dose-dependent and that wash-out by the end of surgery—as suggested by our study—leaves patients at risk for pupil constriction that may affect their surgical outcome (Figure 7).

Compliance with the preoperative regimen in our study was high (92.9%); however, this is not always the case. Ketorolac is known to sting on instillation, and so some patients may skip a dose or else squeeze the eye resulting in lesser instillation. This potential compliance factor, combined with the potential for wash-out we noted in our study, suggests that a different approach may be necessary.

Recently, the US FDA granted approval of OMIDRIA (phenylephrine and ketorolac injection) 1% / 0.3%, an adjunct to the ophthalmic solution and used during cataract surgery to maintain pupil size by preventing miosis and reduce postoperative ocular pain. Both the NSAID and mydriatic components are delivered consistently throughout the procedure. In a canine study in which traditional phacoemulsification and lens placement were performed using OMIDRIA, there was sufficient amount of ketorolac remaining in ocular structures (i.e., sclera, cornea, retina, vitreous, choroid, ciliary body, and iris) to ablate COX-1 and COX-2 pathways for at least 10 hours postoperatively.[3]

The clinical study assessing the washout of topical preoperative NSAID really demonstrated what intuitively makes sense: that topical NSAID delivery before surgery may be less than optimal. This suggests the benefit of using a product infused intracamerally in the irrigation solution, supplying

(Continued on page 10)

OMIDRIA AND MEDICARE REIMBURSEMENT

BY THOMAS A. GUSTAFSON, PHD

OMIDRIA (phenylephrine and ketorolac injection) 1% / 0.3% was recently made commercially available by Omeros Corporation. OMIDRIA is formulated for dilution in standard irrigation solution used during cataract surgery or intraocular lens replacement. This article discusses how OMIDRIA is paid for by Medicare and what implications Medicare's payment has for physicians.

Medicare pays facilities—ambulatory surgery centers and hospital outpatient departments—for OMIDRIA at Average Selling Price plus 6%. This payment is separate from the payment for cataract procedures, which is intended to cover the procedure itself along with any associated drugs or supplies. Because of this additional payment for OMIDRIA, the facility does not have to "eat" the cost within the amount Medicare pays for cataract surgery. The payment formula—Average Selling Price plus 6%—is the same used for injectable drugs furnished in physicians' offices.

The additional payment for OMIDRIA results because CMS has assigned OMIDRIA "transitional pass-through" status. When drugs and devices are in this status, facilities using the designated drugs and devices receive extra payments for these products. Congress established the pass-through provision in the Medicare law in a very explicit and deliberate attempt to encourage the diffusion of new technologies like OMIDRIA as they enter clinical practice. Without such a provision, Medicare's payment systems, because of the rigid and retrospective way in which CMS establishes payment rates, would actually discourage use of new technologies. In setting rates for a particular year, CMS relies on claims from two years earlier: 2015 rates are based on claims from 2013. A newly arriving product is simply not reflected in those claims, and, in the absence of some special provision, it could take years for the cost of the new item to affect significantly the payment rate for the procedure, if such change happens at all. That could severely restrict the diffusion of new technologies into clinical practice. Congress wanted to prevent that result and help new technologies along so Medicare patients could benefit from them.

Medicare's pass-through payments for OMIDRIA do not reduce the payment rates otherwise made to surgeons or to facilities. For surgeons, the pass-through payments do not affect how Medicare pays for the surgeon's services under its Physician Fee Schedule—now or in the future. Physician payment rates are determined separately from the facility payments using a different methodology, and the payments made to facilities do not enter these calculations.

Some physicians have expressed concern that the pass-through payments would somehow enter the calculations for physician payment

WHAT IS PASS THROUGH? A BILLING PERSPECTIVE

By Migdalia "Mindy" Vasquez

A product awarded pass-through status by CMS is one for which reimbursement is separate and distinct from the surgical bundled fee. The payment to the facility for a pass-through product is the Average Selling Price plus a 6% handling fee. In addition to the cataract procedure code, a unique C-code, assigned by CMS to a given pass-through product (e.g., C9447 for OMIDRIA), is used in the billing of the claim to identify the product for reimbursement outside of the bundled or packaged fees.

My past experiences with pass-through products have not been good. In most cases, I found that the vendor did not undertake the necessary procedures to ensure pass-through reimbursement, which resulted in denial of claims and endless appeals processes. My experience with OMIDRIA has been very different and positive, because the company behind the product, Omeros, has done their homework to make sure the reimbursement happens in a timely fashion and at the amount represented. It also has both billing and reimbursement support teams that will assist the facility with its billing process and with securing appropriate reimbursement for OMIDRIA.

When first using OMIDRIA in the facility, as with any new product, I would suggest starting out in a relatively controlled manner and building on the number of cases performed in the facility. At our ambulatory surgery center, we started with one surgeon and then made it standard within the facility. It is also a good idea to keep a close eye on the claims to make sure that they are reimbursed appropriately. As noted previously, the OMIDRIA billing and reimbursement support teams are readily available and willing to answer questions or concerns.

Another practical tip I could offer to other billers is to identify prior to surgery those patients who will be treated with OMIDRIA and apply the orange "OMIDRIA patient" sticker supplied by Omeros to the outside of the patient chart. This will alert the nursing staff to prepare and administer OMIDRIA, which, not coincidentally, comes supplied in a vial with an orange OMIDRIA brand on it. After the procedure is completed, the operative report is stamped "OMIDRIA" (this stamp is also provided by Omeros) to alert the biller to charge the unique C9447 code. I expect that facilities will be surprised at how simple the protocol really is to incorporate OMIDRIA into regular use. ■

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Reimbursement information is based on Omeros data on file. Omeros does not guarantee reimbursement for any particular patient. Contact 1-844-OMEROS1 (1-844-663-7671) for more information about how to submit for OMIDRIA reimbursement.

BILLING FOR OMIDRIA IN AN HOPD OR ASC

By Kevin J. Corcoran, COE, CPC, CPMA, FNAO

Generally speaking, medicines used during surgery are bundled into the facility reimbursement fee and are not separately reimbursable to the ASC or hospital outpatient department (HOPD). Some medicines are eligible for separate reimbursement under a special provision of the Medicare law that addresses new and innovative drugs and devices approved by the FDA.

OMIDRIA (phenylephrine and ketorolac injection) 1% / 0.3%, when used during cataract surgery or lens replacement surgery, may be billed for separate reimbursement under the Part B Medicare Outpatient Prospective Payment System (OPPS) transitional pass-through provision, as established by the Social Security Act §1833(t)(6). Other third-party payers, including Medicare Advantage, may follow CMS' policy but are not obliged to do so.

Current Procedural Terminology (CPT) codes for which providers are eligible to bill Medicare for use of OMIDRIA are summarized in the Table. OMIDRIA is also FDA-approved for use during refractive lens exchange (RLE), however there is no CPT code assigned for this procedure, and Medicare and most third party payers do not cover it, so reimbursement is a moot issue—the patient is financially responsible for all professional and facility fees.

Because of its pass-through status, OMIDRIA is reimbursed by Part B Medicare at a rate above its Average Selling Price (ASP) – the added amount is 6% of ASP and represents a handling fee. It is important to understand that this reimbursement rate for OMIDRIA does not represent a coverage decision; Medicare Administrative Contractors make that determination. Separate reimbursement for OMIDRIA is available under transitional pass-through status until December 31, 2017.

Drugs having pass-through status are subject to the usual 20% Medicare copayment in an ASC but not in an HOPD. Medicare deductibles apply in both settings.

The use of OMIDRIA has no effect on the surgeon's reimbursement or selection of an applicable CPT code. Irrigation in the eye during cataract surgery is an inherent part of the procedure, and there is no separate or distinct professional service or fee for the use of OMIDRIA. Of note, the use of OMIDRIA does not, by itself, support a claim for complex cataract surgery (CPT 66982).

On ASC or HOPD claims for cataract surgery and lens replacement surgery, use HCPCS code C9447 (injection, phenylephrine and ketorolac, 4 ml vial) to identify OMIDRIA in addition to the usual claim for their facility fee. It is advisable for providers and/or their representative billing administrators to seek clarity and guidance from payers regarding billing for OMIDRIA and related services. The guidance provided here is general in nature and does not substitute for guidance received from Medicare or other payers. ■

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CPT Code	Descriptor
66840	Removal of lens material; aspiration technique, 1 or more stages
66850	Removal of lens material; phacofragmentation technique (mechanical or ultrasonic) (e.g., phacoemulsification), with aspiration
66852	Removal of lens material; pars plana approach, with or without vitrectomy
66920	Removal of lens material; intracapsular
66930	Removal of lens material; intracapsular, for dislocated lens
66940	Removal of lens material; extracapsular (other than 66840, 66850, 66852)
66982	Extracapsular cataract removal with insertion of intraocular lens prosthesis (1- stage procedure), manual or mechanical technique … complex, requiring devices or techniques not generally used …
66983	Intracapsular cataract extraction with insertion of intraocular lens prosthesis (1 stage procedure)
66984	Extracapsular cataract removal with insertion of intraocular lens prosthesis (1-stage procedure), manual or mechanical technique …

Table 1. CPT codes matching approved indications for OMIDRIA.

rates either through the Sustainable Growth Rate (SGR) mechanism or through how Medicare calculates practice expenses for physician services. Pass-through payments were not reflected in the SGR calculations, and, in any case, the SGR provisions were repealed by the Medicare and CHIP Reauthorization Act, passed in April 2015.

For facilities, whatever Medicare pays for pass-through payments will not affect the rates Medicare pays for cataract surgery during 2015 and should not materially affect them during the following two years, while facilities receive these temporary payments for OMIDRIA. CMS, in accordance with the pass-through provision in the law, has in essence set aside what we may think of as a pool within the outpatient prospective payment system (OPPS) for paying for all pass-through products. (CMS handles ASC payments for technologies with pass-through status in a comparable fashion.) Other facility payments are reduced very slightly to provide the funding for this virtual pool without increasing Medicare spending. The pool is already set for the year, and whether facilities avail themselves of it will not affect its size—up or down—this year. This pool covers all pass-through items, both drugs and devices; facilities providing services in all specialty areas will draw on it for pass-through items in their respective areas, whether ophthalmologists do or not.

The pool, as compared to total OPPS spending, is small: in 2015, the pool amounted to only 0.13% of overall payments under the OPPS, while over the last decade it has ranged from 0.02% to 0.22% as various products have entered and then left pass-through status. Of these amounts, drugs generally represented about a quarter to a third, while the balance was for devices. In each of the next two years, CMS will redo the pool calculations prior to the beginning of the year to reflect expected utilization of all pass-through products. The extent to which actual utilization

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of OMIDRIA (phenylephrine and ketorolac injection) 1% / 0.3% will affect these estimates, up or down, is unclear; there might be no change or, considering OMIDRIA is only one product that enters these calculations and the impact is spread over all payments under the OPPS, the effect may be minimal.

Although the amount Medicare pays for OMIDRIA for an individual procedure may seem large, it is important to recognize that the size of the pass-through pool is not large relative to Medicare spending. Medicare outlays are now about $500 billion a year, and pass-through payments in general, and OMIDRIA payments in particular, are a very small fraction of this total.

After 2017, when the pass-through period for OMIDRIA is over, CMS has indicated its intention to package the drug with cataract surgery.[1] Assuming it does so, facility payment rates for cataract surgery will rise to reflect how extensively OMIDRIA is used in hospitals in the meantime.

Some have expressed concern about whether the pass-through payments are fueling the fire of growth in health care costs. Health care has been one of the more aggressively growing sectors of the economy for decades. However, in the past 5 years, health care spending has grown at historically low rates. In 2013, the most recent year for which information is available, CMS actuaries calculated that US health care spending increased by 3.6%, 0.5% less than in 2012. Medicare spending growth fell from 4.0% to 3.4% in the same interval.[2] Whether higher rates will reemerge in the future is, of course, speculative, but the pass-through provision is budget neutral and pass-through payments, which have existed before and during this slow down, are unlikely to be a significant factor in any future upticks in spending growth.

In general, we do need to recognize the legitimacy of the concern about growing health care costs and the growth in Medicare outlays in particular. However, allowing Medicare patients to access and receive the benefits of technological improvements in care remains an important goal of the Medicare program. Both issues matter, and Congress has attempted to balance the goals of constraining outlays and of facilitating access to clinical improvements.

Congress obviously must be concerned about overall spending, and each year it wrestles with the impact of Medicare on the federal budget. In recent years, Congress also has added several provisions to the Medicare law to facilitate access to new technology, including the pass-through provision. Note that in the most recent major Medicare bill—which repealed the SGR—Congress, while it introduced several provisions aimed at controlling Medicare expenditures over time, did not roll back any of the provisions providing incentives for new technologies.

It is also important to be careful about applying a "macro" argument to a "micro" issue. What surgeons and facilities do in adopting a particular pass-through product such as OMIDRIA, on the one hand, will not meaningfully affect overall growth in Medicare outlays, on the other. This is because Congress has set up the pass-through payment provision to be budget neutral, and CMS sets the applicable payment rates so use of pass-through products by providers is not expected to increase overall spending.

In sum, Medicare wants to encourage use of pass-through products, such as OMIDRIA, to make the benefits of innovative technological changes available for its beneficiaries. Accordingly, during the pass-through period, Medicare offers a facility the opportunity of receiving an extra payment when it uses OMIDRIA. These payments are drawn from a "pool" that CMS has set up to cover all pass-through products, and all specialty areas have the opportunity to tap the pool when using these products. As is noted above, surgeons' professional fees are unaffected by these changes. Because of the pass-through provision's budget neutrality requirement, effects on overall spending should be negligible, and facilities should not be concerned about these payments materially reducing their fees for cataract surgical procedures. Once the pass-through period is over and assuming CMS packages OMIDRIA with the cataract surgery procedures, facility surgical fees will rise to reflect utilization of the product while it was in pass-through status. ■

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- Financial disclosure: none acknowledged
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1. DHHS. Transitional pass-through for additional costs of innovative medical devices, drugs, and biologicals. *Federal Register.* 2000;65(68):15:18438.
2. Hartman M, Martin AB, Lassman M, et al. National health spending in 2013: Growth slows, remains instep with the overall economy. *Health Aff.* January 2015.

(Continued from page 7)

steady and predictable amounts of a nonsteroidal throughout the case. The NSAID is, therefore, likely to have a durable effect that will reduce the potential impact of miosis and reduce postoperative pain—potentially reducing or eliminating the so-called second eye phenomenon we frequently see with patients undergoing cataract surgery. In my experience, I have seen a reduction in patients reporting pain in their second procedure when I have used OMIDRIA.

Another observation in connection with the use of OMIDRIA in my clinic is the impact on efficiency since starting to use OMIDRIA about 6 months ago. On surgical days, I still perform the same number of cases as before, but I find myself routinely completing my cases about an hour earlier than usual—and I really only use OMIDRIA in about half of my cases at present. I have already noticed a dramatic difference in difficult cases, because there is less guess work and I feel more confident that I can maneuver through the anterior chamber. I expect my overall time in the OR to go down even more as I ramp up use of OMIDRIA in my clinic.

CONCLUSION

Use of OMIDRIA, in my opinion, has made my surgery days predictable and efficient. Unlike preoperative topical drops, OMIDRIA is delivered in the irrigation solution directly to the anterior chamber in a steady-state concentration throughout the procedure. Our study demonstrated that if topical NSAIDs are used prior to cataract surgery, they will likely not be present by the end of the case. The use of OMIDRIA, containing both phenylephrine and ketorolac, added to the irrigation will (1) provide adequate concentrations of both agents to maintain mydriasis and to prevent miosis, and (2) have lasting postoperative effects as evidenced by the ketorolac-driven reduction in postoperative pain. In my hands, the use of OMIDRIA during the procedure gives me confidence that I am doing everything possible to reduce the potential impact of miosis and postoperative pain on patients' surgical results. ■

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1. Drews RC, Katsev DA. Ocufen and pupillary dilation during cataract surgery. *J Cataract Refract Surg* 1989;15:445–448.
2. Katsev D, Katsev C, Pinnow J. Intracameral Ketorolac Concentration After Topical Ketorolac Administration Prior to Cataract Surgery. Electronic poster session presented at: American Society of Cataract and Refractive Surgery. 2015 ASCRS-ASOA Symposium and Congress; 2015 Apr 17–21; San Diego, CA.
3. Florio V, Cowan L, Prusakiewicz JJ, Bentley E, Waterbury, LD. Ocular tissue distribution of ketorolac after administration of OMS302 to dogs during IOL replacement. Electronic poster session presented at: American Society of Cataract and Refractive Surgery. 2015 ASCRS-ASOA Symposium and Congress; 2015 April 17–21; San Diego, CA.

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OMIDRIA® safely and effectively. See full prescribing information for OMIDRIA.

OMIDRIA® (phenylephrine and ketorolac injection) 1% / 0.3%
Initial U.S. Approval: 2014

INDICATIONS AND USAGE

OMIDRIA is an alpha 1-adrenergic receptor agonist and nonselective cyclooxygenase inhibitor indicated for:

- Maintaining pupil size by preventing intraoperative miosis (1)
- Reducing postoperative pain (1)

OMIDRIA is added to an irrigation solution used during cataract surgery or intraocular lens replacement.

DOSAGE AND ADMINISTRATION

OMIDRIA must be diluted prior to use. For administration to patients undergoing cataract surgery or intraocular lens replacement, 4 mL of OMIDRIA is diluted in 500 mL of ophthalmic irrigating solution. Irrigation solution is to be used as needed for the surgical procedure. (2)

DOSAGE FORMS AND STRENGTHS

OMIDRIA is a sterile solution concentrate containing 1% w/v of phenylephrine and 0.3% w/v ketorolac in a single-patient-use vial. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

Systemic exposure of phenylephrine may cause elevations in blood pressure. (5.1)

ADVERSE REACTIONS

The most common reported adverse reactions at 2-24% are eye irritation, posterior capsule opacification, increased intraocular pressure, and anterior chamber inflammation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Omeros Corporation at 1-844-OMEROS1 or *www.omidria.com* or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

See 17 for PATIENT COUNSELING INFORMATION

Revised: June 2015

FULL PRESCRIBING INFORMATION: CONTENTS*

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FULL PRESCRIBING INFORMATION:

1 INDICATIONS AND USAGE

Omidria® 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 ocular pain.

2 DOSAGE AND ADMINISTRATION

Omidria must be diluted prior to intraocular use. For administration to patients undergoing cataract surgery or intraocular lens replacement, 4 mL of Omidria is diluted in 500 mL of ophthalmic irrigation solution. Irrigation solution is to be used as needed for the surgical procedure.

The storage period for the diluted product is not more than 4 hours at room temperature or 24 hours under refrigerated conditions.

Do not use if the solution is cloudy or if it contains particulate matter.

3 DOSAGE FORMS AND STRENGTHS

Omidria is a sterile solution concentrate containing 10.16 mg/mL (1% w/v) of phenylephrine and 2.88 mg/mL (0.3% w/v) of ketorolac in a single-patient-use vial.

4 CONTRAINDICATIONS

Omidria is contraindicated in patients with a known hypersensitivity to any of its ingredients.

5 WARNINGS AND PRECAUTIONS

5.1 Elevated Blood Pressure

Systemic exposure of phenylephrine can cause elevations in blood pressure.

5.2 Cross-Sensitivity or Hypersensitivity

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other non-steroidal anti-inflammatories (NSAIDs). There have been reports of bronchospasm or exacerbation of asthma associated with the use of ketorolac in patients who either have a known hypersensitivity to aspirin/NSAIDs or a past medical history of asthma. Therefore, use Omidria with caution in individuals who have previously exhibited sensitivities to these drugs.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to the rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Table 1 shows frequently reported ocular adverse reactions with an incidence of ≥ 2% of subjects as seen in the combined clinical trial results from three randomized, placebo-controlled studies.

Table 1: Ocular Adverse Reactions Reported by ≥ 2% of Subjects

MedDRA Preferred Term	Placebo (N=462)	Omidria (N=459)
	n (%)	n (%)
Ocular Events		
Anterior Chamber Inflammation	102 (22%)	111 (24%)
Intraocular Pressure Increased	15 (3%)	20 (4%)
Posterior Capsule Opacification	16 (4%)	18 (4%)
Eye Irritation	6 (1%)	9 (2%)
Foreign Body Sensation in Eyes	11 (2%)	8 (2%)

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: 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 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 1.5 mg/kg/day (740 times the plasma exposure at the RHOD), ketorolac produced dystocia and increased pup mortality.

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.

8.3 Nursing Mothers

Because many drugs are excreted in human milk, caution should be exercised when Omidria is administered to nursing women.

8.4 Pediatric Use

Safety and effectiveness of Omidria in pediatric patients below the age of 18 years have not been established.

8.5 Geriatric Use

No overall differences in safety or effectiveness have been observed between elderly and adult patients.

10 OVERDOSAGE

Systemic overdosage of phenylephrine may cause a rise in blood pressure. It may also cause headache, anxiety, nausea, vomiting, and ventricular arrhythmias. Supportive care is recommended.

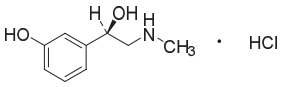
11 DESCRIPTION

Omidria is a sterile aqueous solution concentrate containing the α_1-adrenergic receptor agonist phenylephrine HCl and the nonsteroidal anti-inflammatory ketorolac tromethamine.

The descriptions and structural formulae are:

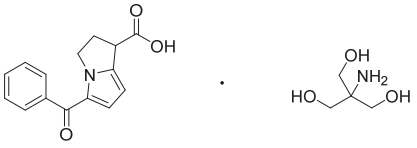
Phenylephrine Hydrochloride Drug Substance:
Common Name: phenylephrine hydrochloride
Chemical Name: (-)-*m*-Hydroxy-α-[(methylamino)methyl]benzyl alcohol hydrochloride
Molecular Formula: $C_9H_{13}NO_2 \cdot HCl$
Molecular Weight: 203.67 g/mole

Figure 1: Chemical Structure for Phenylephrine HCl



Ketorolac Tromethamine Drug Substance:
Common Name: ketorolac tromethamine
Chemical Name: (±)-5-Benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid : 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1)
Molecular Formula: $C_{15}H_{13}NO_3 \cdot C_4H_{11}NO_3$
Molecular Weight: 376.40 g/mole

Figure 2: Chemical Structure for Ketorolac Tromethamine



Omidria is a clear, colorless to slightly yellow, sterile solution concentrate with a pH of approximately 6.3.

Each vial of Omidria contains:

Actives: phenylephrine hydrochloride 12.4 mg/mL equivalent to 10.16 mg/mL of phenylephrine and ketorolac tromethamine 4.24 mg/mL equivalent to 2.88 mg/mL of ketorolac.

Inactives: citric acid monohydrate; sodium citrate dihydrate; water for injection; may include sodium hydroxide and/or hydrochloric acid for pH adjustment.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The two active pharmaceutical ingredients (API) in Omidria, phenylephrine and ketorolac, act to maintain pupil size by preventing intraoperative miosis, and reducing postoperative pain.

Phenylephrine is an α_1-adrenergic receptor agonist and, in the eye, acts as a mydriatic agent by contracting the radial muscle of the iris. Ketorolac is a nonsteroidal anti-inflammatory that inhibits both cyclooxygenase enzymes (COX-1 and COX-2), resulting in a decrease in tissue concentrations of prostaglandins to reduce pain due to surgical trauma. Ketorolac, by inhibiting prostaglandin synthesis secondary to ocular surgical insult or direct mechanical stimulation of the iris, also prevents surgically induced miosis.

12.3 Pharmacokinetics

In a pharmacokinetic study evaluating Omidria, systemic exposure to both phenylephrine and ketorolac was low or undetectable.

A single-dose of Omidria as part of the irrigation solution was administered in 14 patients during lens replacement surgery. The volume of irrigation solution used during surgery ranged between 150 mL to 300 mL (median 212.5 mL). Detectable phenylephrine plasma concentrations were observed in one of 14 subjects (range 1.2 to 1.4 ng/mL) during the first two hours after the initiation of Omidria administration. The observed phenylephrine plasma concentrations could not be distinguished from the preoperative administration of phenylephrine 2.5% ophthalmic solution prior to exposure to Omidria.

Ketorolac plasma concentrations were detected in 10 of 14 subjects (range 1.0 to 4.2 ng/mL) during the first 8 hours after the initiation of Omidria administration. The maximum ketorolac concentration was 15 ng/mL at 24 hours after the initiation of Omidria administration, which may have been due to application of postoperative ketorolac ophthalmic solution.

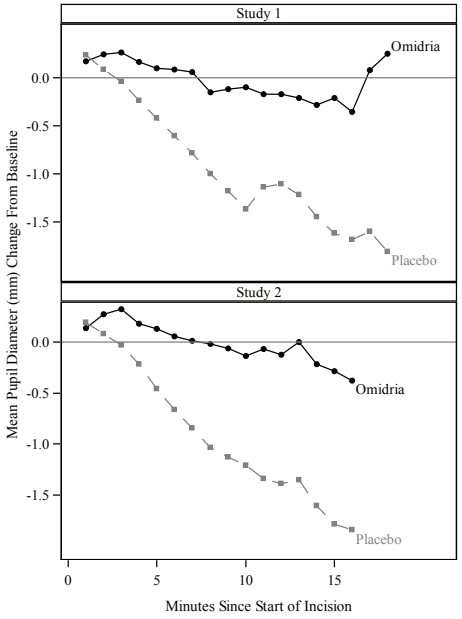
14 CLINICAL STUDIES

The efficacy and safety of Omidria were evaluated in two Phase 3, randomized, multicenter, double-masked, placebo-controlled clinical trials in 808 adult subjects undergoing cataract surgery or intraocular lens replacement.

Subjects were randomized to either Omidria or placebo. Subjects were treated with preoperative topical mydriatic and anesthetic agents. Pupil diameter was measured throughout the surgical procedure. Postoperative pain was evaluated by self-administered 0-100 mm visual analog scales (VAS).

Mydriasis was maintained in the Omidria-treated groups while the placebo-treated groups experienced progressive constriction.

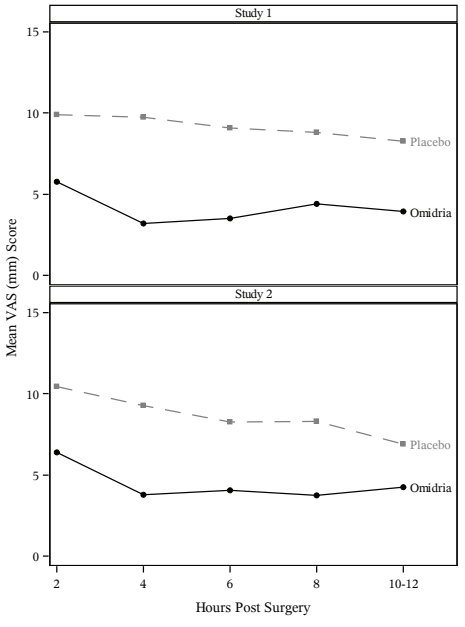
Figure 3: Intraoperative Pupil Diameter (mm) Change-from-Baseline



At the end of cortical clean-up, 23% of placebo-treated subjects and 4% of Omidria-treated subjects had a pupil diameter less than 6 mm ($p < 0.01$).

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

Figure 4: Postoperative Mean Visual Analog Scale (VAS) Scores for Pain



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

16 HOW SUPPLIED/STORAGE AND HANDLING

Omidria is supplied as a sterile solution concentrate in a clear, 5-mL glass, single-patient-use vial containing 4 mL of sterile solution.

Omidria is supplied in a multi-pack containing:
4 single-patient-use vials: NDC 62225-600-04 or 10 single-patient-use vials: NDC 62225-600-10

Storage: Store at 20° to 25°C (68° to 77°F). Protect from light.

17 PATIENT COUNSELING INFORMATION

Inform patients that they may experience sensitivity to light.

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US Patents 8,173,707 and 8,586,633; additional patents pending. Revised: 06/2015